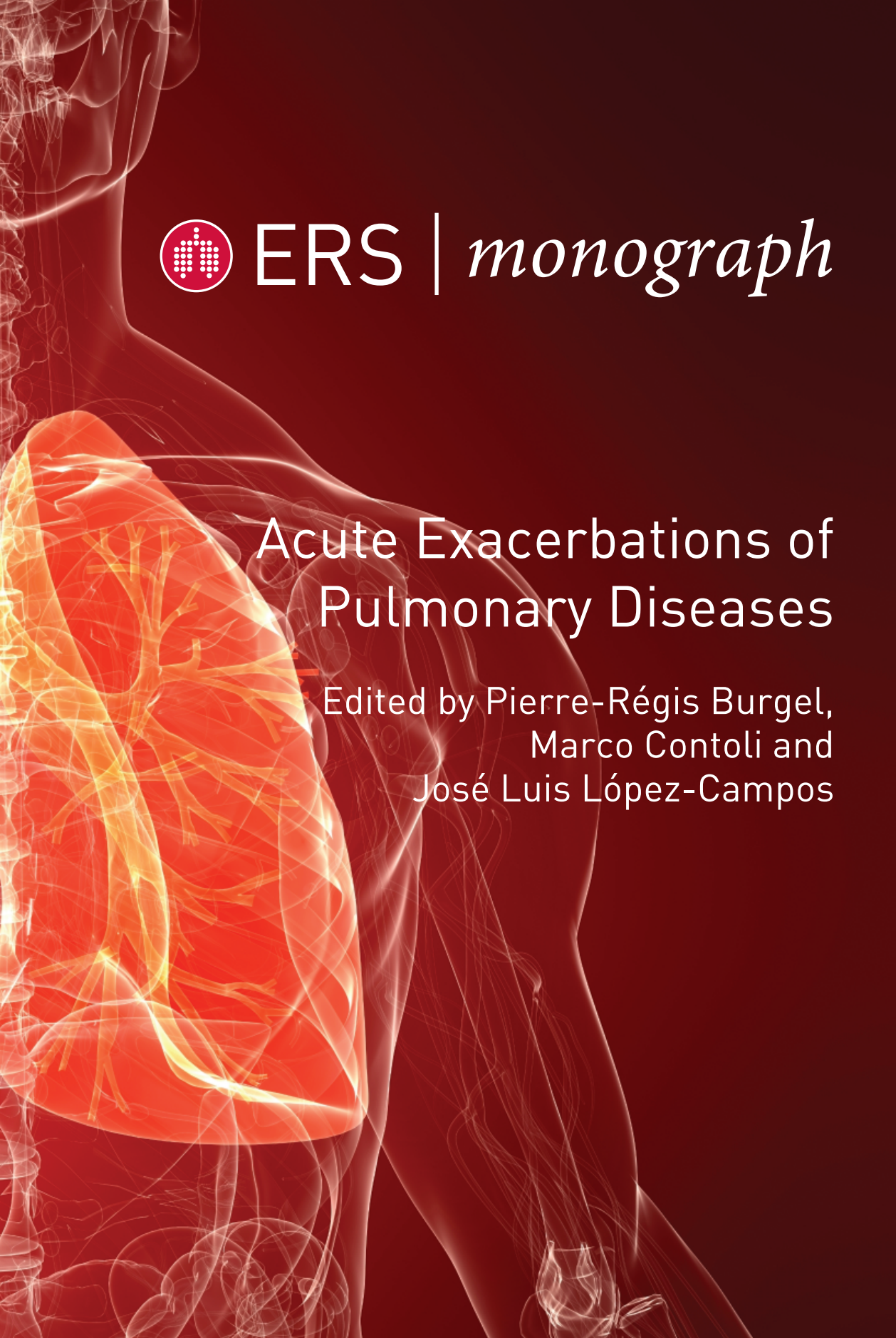
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Acute Exacerbations of Pulmonary Diseases
Edited by Pierre-Régis Burgel, Marco Contoli and José Luis López-Campos

Acute Exacerbations of Pulmonary Diseases

Edited by
Pierre-Régis Burgel, Marco Contoli
and José Luis López-Campos

Editor in Chief
Robert Bals

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Published by European Respiratory Society ©2017
September 2017
Print ISBN: 978-1-84984-089-7
Online ISBN: 978-1-84984-090-3
Print ISSN: 2312-508X
Online ISSN: 2312-5098
Typesetting by Nova Techset Private Limited
Printed by Ashford Colour Press Limited

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September 2017

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Preface

Robert Bals

Many lung diseases have a chronic course, and this in itself can be challenging to manage. Diseases like COPD and IPF, for example, slowly deteriorate and treatment is often limited to relieving symptoms. It is disastrous for the patient if the situation gets out of control and the disease gets much worse within a short time. It is often difficult to understand the underlying biological processes of these deteriorations. Exacerbations frequently result in a faster decline of the underlying disease and can cause the death of the patient. The field of exacerbations in pulmonary diseases is complex and inadequately understood, for a number of reasons: 1) Generally, the pathomechanisms of exacerbations are poorly understood. 2) The definitions of exacerbations are often unclear, which can cause additional difficulties in the diagnosis of these sudden deteriorations. 3) It is often difficult to rule out relevant differential diagnoses and in many cases, these seem to be more than one disease entity, including infections. 4) Treatment options can be very limited, which is largely a result of a lack of basic understanding of what is happening.

Whilst all of this may seem pessimistic, this area actually provides an opportunity to improve the care of our patients. Exacerbations represent an acute-on-chronic condition and it should be possible to focus future research on mechanisms, diagnosis and treatment. In addition, there is clearly a need to raise awareness about these critical conditions in pulmonary medicine. In comparison with the number of chest pain and stroke units, very few departments handle exacerbations of respiratory diseases in a similar treatment structure, despite the fact that pulmonary exacerbations have a significant impact on the patient and on mortality figures overall.

This *Monograph* provides a comprehensive overview of exacerbations in pulmonary diseases. It covers specific disease entities such as COPD, asthma, CF and IPF, and provides detailed information for the clinician. It also discusses the mechanisms of exacerbation development, which is an important for the prevention of and basic understanding about this area.

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The Guest Editors, Pierre-Régis Burgel, Marco Contoli and José Luis López-Campos, have selected and integrated the topics covered to create a book that successfully summarises current knowledge in this area. I thank the Guest Editors and all of the authors for their hard work on this excellent book. Together, they have produced a practice-guideline publication, comprising information about scientific background and application at the patient's bedside. I am sure that this comprehensive review will prove useful in the clinical practice of a broad range of respiratory physicians, and will improve the care of patients that experience AEs.

Disclosures: R. Bals has received grants from the German Research Ministerium and the Deutsche Forschungsgemeinschaft. He has also received personal fees from GSK, AstraZeneca, Boehringer Ingelheim and CSL Behring.

https://doi.org/10.1183/2312508X.10012617

Guest Editors

Pierre-Régis Burgel

Pierre-Régis Burgel is currently Professor of Respiratory Medicine at Paris Descartes University in Paris, France, where he is also a senior researcher in the Cystic Fibrosis and Chronic Airway Diseases Laboratory. He is a senior consultant at the Respiratory Medicine Department of Cochin Hospital in Paris.

Pierre-Régis Burgel completed his medical training at the University of Paris, School of Medicine (Paris), in 1999. After a post-doctoral fellowship at the University of California in San Francisco (USA) (1999–2001), he obtained a PhD in respiratory cell biology at the University of Paris. His main research interests include COPD phenotypes, CF in adults, and chronic bacterial infection in COPD and CF. He has published over 150 articles in peer reviewed journals in these areas of lung disease.

Pierre-Régis Burgel is a member of several professional societies, including the European Respiratory Society (ERS), the American Thoracic Society (ATS), the European Cystic Fibrosis Society (ECFS), and the Société de Pneumologie de Langue Francaise (SPLF). He is Vice President of the French Cystic Fibrosis Society and a member of the ERS College of Experts. He is also a member of the Editorial Boards of the *European Respiratory Journal*, *COPD: Journal of Chronic Obstructive Pulmonary Disease* and *Revue des Maladies Respiratoires*. He is the scientific secretary of the French collaborative group INITIATIVES BPCO, which is dedicated to the identification of clinically relevant COPD phenotypes. He was recently an active member of the ATS/ERS task force on Research Questions in COPD and the ERS/ECFS task force on the Provision of Care for Adults with CF in Europe.

Marco Contoli

Marco Contoli is Assistant Professor at the Section of Respiratory Diseases, Dept of Medical Sciences, of the University of Ferrara, Ferrara, Italy. He is also a respiratory consultant at the Respiratory Disease Unit of the Arcispedale Sant'Anna, Azienda Ospedaliero-Universitaria (Ferrara).

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He gained his degree in medicine and surgery at the University of Bologna (Bologna, Italy) in 2001. He went on to study respiratory diseases at the University of Ferrara (Ferrara, Italy) and a PhD in Experimental Respiratory Pathophysiology at the University of Parma (Parma, Italy). As a recipient of a European Respiratory Society (ERS) fellowship, he spent 1 year (November 2003–November 2004) working in Professor Sebastian Johnston's laboratory at St Mary's Hospital (Imperial College, London, UK).

Marco Contoli's main clinical expertise is in the diagnosis, management and treatment of asthma and COPD. His research interests include mechanisms of virus-induced exacerbations of asthma and COPD, markers of airway inflammation and mechanisms of airways obstruction, and the impact of comorbid conditions in asthma and COPD. He has served as co-investigator in several clinical and pharmacological international trials conducted according to good clinical practice guidelines in the field of asthma and COPD. He has published research in leading international journals and serves as invited reviewer for the most important respiratory journals. He is a member of the ERS.

José Luis López-Campos

José Luis López-Campos is a pulmonologist at the Hospital Universitario Virgen del Rocío (Seville, Spain), and is the head of the monographic COPD and the bronchiectasis outpatient clinic. He also serves as Associate Professor of Medicine at the University of Seville (Seville) and tutors residents of pneumology at the Hospital Universitario Virgen del Rocío. He is head of a research group linked to the CIBER of Respiratory Diseases, Ministry of Economy, Spain. His research projects include epidemiology, clinical audits and translational research in COPD.

As well as serving as an Associate Editor of *Archivos de Bronconeumología*, José Luis Lopez-Campos is Chair of the Monitoring Airway Disease group of the European Respiratory Society (ERS) and is a member of the ERS College of Experts. He was previously: secretary of the COPD Assembly at the Spanish national society (SEPAR); Web Director at SEPAR; and ERS Clinical Assembly web coordinator.

Recent publications have included research on T-helper type 2 signatures in chronic airway diseases (with the CHACOS study group), results from the Andalusian COPD audit and a study of the effects of smoke-free legislation on lung cancer mortality trends.

https://doi.org/10.1183/2312508X.10010617

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Introduction

Pierre-Régis Burgel[1,2], Marco Contoli[3] and José Luis López-Campos[4,5]

Chronic non-communicable respiratory diseases (*e.g.* asthma, COPD, CF, bronchiectasis and IPF) are responsible for high morbidity and mortality. These diseases represent a significant burden to patients and healthcare systems, and are considered a major challenge in the currently ageing population worldwide. Despite their differences in nature, chronic respiratory diseases all have one thing in common: a considerable impact on patient health status, which mainly derives from the impact of symptoms in the short and the long term. AEs of chronic respiratory diseases are also no longer considered to be just an increase in symptoms. On the contrary, it has now been established that exacerbations are associated with significant immediate risks (*e.g.* hospitalisation and/or death) and are responsible for a deep long-term impact with prognostic implications.

The field of AEs in chronic respiratory diseases is challenging. Definitions of AEs differ amongst the diseases, as investigators have used various combinations of symptoms and/or biomarkers (*e.g.* imaging, lung function), which were often based on expert opinion or data availability. Similarly, the severity of exacerbations has proven challenging to define, as these definitions of severity often rely on therapeutic management (*e.g.* the need for specific drugs and/or hospitalisation), which may have varied in different countries with different healthcare systems. Major progress has therefore been the establishment of a consensus for diagnosing and establishing the severity of exacerbations in each individual disease, allowing for comparisons among studies and the development of therapeutic strategies. In this regard, some fields have evolved rapidly (*e.g.* asthma and COPD), whereas the concept of exacerbations is emerging more slowly in other diseases (*e.g.* CF, bronchiectasis and IPF).

In the present issue of the *ERS Monograph*, we have brought together a series of articles from internationally recognised experts in the field of exacerbations in chronic lung diseases. The book is separated into three sections: the first section considers the definition, severity and consequences of exacerbations in each disease. The second section looks at exacerbation triggers, including bacterial and viral infections, air pollution and allergen exposure; part of this section is also dedicated to the difficult problem of differential diagnosis of exacerbations, which should not be confounded with other acute conditions (*e.g.* left heart failure or pulmonary embolism). The last section discusses the treatment and

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

prevention of exacerbations using pharmacological and non-pharmacological interventions (*e.g.* pulmonary rehabilitation and strategies aimed at improving physical activity).

The book's originality lies in the fact that it covers AEs in various respiratory diseases, allowing comparisons between definitions, short- and long-term consequences, triggers and therapeutic management. As such, this book will serve as a complete and up-to-date reference that will raise awareness on the importance of exacerbations in patients with chronic lung diseases and will promote further research in this area.

Disclosures: P-R. Burgel has received personal fees from the following, outside the submitted work: AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Vertex, Aptalis and Zambon. M. Contoli reports receiving a grant from GlaxoSmithKline during the conduct of the study and a grant from Chiesi outside the submitted work. M. Contoli reports receiving personal fees from the following, outside the submitted work: Chiesi, AstraZeneca, Boehringer Ingelheim, Chiesi, AstraZeneca, Novartis, Menarini, Mundipharma, Almirall and Zambon.

 https://doi.org/10.1183/2312508X.10010417

List of abbreviations

AE	acute exacerbation
CF	cystic fibrosis
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
HRCT	high-resolution computed tomography
ICU	intensive care unit
IL	interleukin
IPF	idiopathic pulmonary fibrosis
MRSA	methicillin-resistant *Staphylococcus aureus*
NTM	nontuberculous mycobacteria
P_{aCO_2}	arterial carbon dioxide tension
P_{aO_2}	arterial oxygen tension
QoL	quality of life
RCT	randomised controlled trials
S_{aO_2}	arterial oxygen saturation
TNF	tumour necrosis factor

Asthma: definition, severity and impact of pulmonary exacerbations

Luca Morandi, Federico Bellini and Alberto Papi

Asthma is one of the most common chronic respiratory diseases worldwide. The natural history of the disease is punctuated by episodes of symptom worsening, termed exacerbations. These play an important role in the natural history of the disease, in terms of their effect on morbidity and mortality and because of the economic healthcare burden. Exacerbations are generally acute or subacute in presentation and may, in some cases, represent the initial presentation of bronchial asthma. Clinically, it is important to understand and recognise the risk factors involved in triggering an acute event. When facing a patient with suspected exacerbated asthma, clinicians must first exclude a diagnosis other than asthma and then identify potential risks for asthma-related death and assess the clinical severity of the manifestations. Proper asthma management and treatment should primarily aim to prevent and reduce, and possibly eradicate, exacerbation episodes.

Cite as: Morandi L, Bellini F, Papi A. Asthma: definition, severity and impact of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 1–12 [https://doi.org/10.1183/2312508X.10015516].

Asthma is one of the most common chronic respiratory diseases worldwide, affecting about 10% of the adult population [1, 2]. Its prevalence varies widely and is reported to be between 1% and 18% among different countries [3]. It is estimated that about 300 million people worldwide are affected by bronchial asthma, with an increase of 100 million asthmatic patients expected by 2025 [3, 4].

Definition and epidemiology

The global prevalence of self-reported, doctor-diagnosed asthma in adults is 4.3%, and is higher in developed countries and lower in developing countries [5]. It is likely that there is an underestimation of asthma prevalence in poorer countries due to the poor availability of medications and the difficulties in accessing healthcare. Asthma prevalence is considered to be stable or decreasing in many developed countries, while prevalence is still increasing in developing countries [6].

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The incidence of asthma in children up to 5 years of age is ~23 per 1000 population per year, and decreases to ~4.4 per 1000 per year in young people between 12 and 17 years of age. In adults, the incidence in women is ~1.8 times that in men (4.9 per 1000 *versus* 2.8 per 1000, respectively), while in adolescence, prevalence is higher in boys than girls [7].

Asthma is a clinically heterogeneous disease in terms of the severity of the manifestations and of chronicity/recurrence of the symptomatology and the frequency/severity of acute episodes [1, 8–10]. The severity of the disease varies from mild to severe, and is based on the level of treatment required to get the disease under control and maintain this control. Severe asthma is defined as asthma requiring treatment with high-dose inhaled corticosteroids (ICSs), plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled", or asthma that remains "uncontrolled" despite this therapy [11].

The natural history of the disease is punctuated by recurrent episodes of worsening in symptoms, termed exacerbations. Asthma exacerbations, also called "asthma attacks" or "flare-ups", can be defined as episodes characterised by a progressive increase in or development of asthma symptoms, such as increasing cough with or without sputum production, wheezing, chest tightness, shortness of breath and dyspnoea, accompanied by a reduction in lung function with consequent loss of asthma control, requiring a change in treatment [1]. Exacerbations can develop at any time and at any level of asthma severity. The frequency of exacerbations among asthmatics varies with factors such as age, sex, asthma phenotype, exposure to environmental triggers and disease severity.

In children, exacerbations are more frequent in males, while in adulthood, women are at higher risk for exacerbation. The reason for this has not been determined, but a relationship with sex hormones has been postulated [12]. Different seasonality peaks in asthma exacerbations can occur between children and adults. Studies involving different countries have shown that the number of hospital visits for exacerbated asthma in children increases in September soon after reopening of the schools (the so-called September epidemic) [13, 14]. In most studies, this seasonal pattern has been attributed to a synergistic effect between treatment withdrawal that can occur during the summer and rhinovirus epidemics that occur in this period of the year [13, 14]. Similar studies conducted in the adult population have not shown strong evidence of a seasonal peak in exacerbations, with exacerbations occurring throughout the year [12].

Studies have shown that some asthma phenotypes are more prone to develop exacerbations. In particular, eosinophilic asthma [15] and early-onset atopic asthma [16, 17] present an increased risk of a high exacerbation rate (up to 3.4 and 4.6 exacerbations per year, respectively). Deficient innate immune responses have also been proposed as risk factors of frequent/severe exacerbation episodes in some groups of asthma patients [18].

Moreover, although AEs can occur at any level of severity of bronchial asthma, they are more common in severely asthmatic patients [19].

In the Global Initiative for Asthma (GINA) report, the two main outcomes recommended for appropriate management of asthma are asthma symptom control and reduction of exacerbations [1]. Indeed, control of symptoms has been shown to relate to future exacerbation risk in the general population. These results were confirmed by a retrospective analysis by Bateman *et al.* [20], who studied the relationship between asthma control evaluated by the Asthma Control Questionnaire (5-item version) and the future risk of

 https://doi.org/10.1183/2312508X.10015516

instability and exacerbations. The authors found that better asthma control was associated with a significantly reduced risk for exacerbation.

A *post-hoc* analysis of the GOAL (Gaining optimal asthma control) study demonstrated that, once asthma control is achieved for 8 weeks, this can greatly reduce the probability of it becoming uncontrolled, and that a higher stability in asthma control is also associated with a lower future probability of unscheduled healthcare resource use and better QoL [21].

However, the GINA report also underlines how some patients experience exacerbations despite good symptom control [1]. Risk factors that increase the risk of exacerbations in asthmatic patients include uncontrolled asthma symptoms, high short-acting β_2-agonist use, absence/poor adherence or incorrect use of ICSs, low FEV_1, major socioeconomic problems, exposure to smoke and allergens, main comorbidities (*e.g.* obesity, rhinosinusitis and allergy), sputum or blood eosinophilia, pregnancy, previous access to the ICU for asthma, and one or more severe exacerbations in the previous year [1].

The burden of exacerbations: global impact and costs

Asthma exacerbations represent key elements in the natural history of the disease, in terms of both their impact on morbidity and mortality and the proportion of resources that they absorb among healthcare expenses for asthma [22].

Exacerbations have a negative impact on asthma prognosis and represent one of the most frequent causes of hospitalisation for asthmatic patients [1, 19, 22, 23]; their reduction represents a key element in asthma management, as recognised by national and international guidelines.

In Europe, ~30 million people are affected by bronchial asthma, and it is estimated that ~15 000 people die each year as a result of this disease [3, 24, 25]. Asthma death can be considered the most severe expression of acute asthma. According to World Health Organization estimates, approximately 250 000 people die prematurely each year as a result of asthma [26]. The Royal College of Physicians reported 195 deaths attributable to asthma in the period between February 2012 and January 2013 in the UK [27]. This report showed that 57% of these patients were not recorded as being under specialist supervision in the previous year. Notably, 47% of patients who died had a history of a previous hospital admission for asthma [27].

Overall, however, asthma-related mortality in Europe and the USA has decreased significantly over the last 20–30 years [28, 29]. Several factors have been proposed to explain this decrease in asthma mortality and morbidity, including increased overall disease awareness, improved recognition and control of trigger factors, and improvement and optimisation of therapeutic regimens [10, 30, 31].

A meta-analysis by Lasserson *et al.* [32] in a population of nonsevere asthmatic patients reported an exacerbation rate (requiring the use of systemic steroids) of 0.2 events per year. However, another study by Bousquet *et al.* [33] showed that in severe asthma there may be higher exacerbation rates of up to 1.4 per year. Other studies have estimated that the rate of exacerbation can range from ~0.34 to 0.92 per patient per year, depending on the severity of the disease and on the level of therapy [34, 35]. Chipps *et al.* [36] in the TENOR (The

epidemiology and natural history of asthma: outcomes and treatment regimens) study, a real-life prospective study, analysed patients with severe or difficult-to-treat asthma and demonstrated high rates of healthcare use in this group of patients. They also showed that patients with uncontrolled asthma or a history of exacerbations were at higher risk of future exacerbations [36]. Similarly, the Severe Asthma Research Program (SARP), analysing clinical characteristics of severely asthmatic patients, found a significantly different rate of access to the emergency department in different degrees of asthma severity (40% among severe asthmatics *versus* 20% in moderate asthmatics and 15% in mild asthmatics) [37]. In this study, patients with refractory asthma (*i.e.* asthmatic patients in which control is not achieved despite maximal therapy) experienced up to four episodes of severe exacerbations per year, and 25% of these events required hospitalisation [38].

It has been calculated that severely asthmatic patients are responsible for the vast majority of disease-related health costs. In particular, exacerbations, and even more significantly hospitalisations, contribute to increase the asthma-related costs [39–44]. Patients with one or more exacerbations per year had significantly higher total healthcare costs (USD9223 *versus* USD5011; $p<0.0001$) and asthma-related costs (USD1740 *versus* USD847; $p<0.0001$) compared with nonexacerbated patients [45]. Treatment of exacerbations represents 80% of the total direct costs of asthma [46].

The global cost for the management of severe asthma is expected to increase in the next few years because of the introduction of new biological drugs as treatment for selected phenotypes of refractory disease [10]. Notably, a reduction in exacerbation rate was the primary efficacy outcome of pivotal studies testing the efficacy of several new biologics (including anti-IL-5, anti-IL-5 receptor a, anti-IL-4 receptor a and anti-IL-13) [10]. Not only do exacerbations of asthma represent a relevant cause of premature deaths and major expense for healthcare systems, they also have an impact on relevant clinical outcomes in the natural history of the disease, such as progression of the disease, QoL and loss of productivity.

Bai *et al.* [47] studied a cohort of 93 nonsmoking asthmatic patients with moderate-to-severe disease prior to treatment with ICSs for ⩾5 years (median follow-up 11 years) and found that 60% of subjects experienced at least one severe exacerbation. The use of oral corticosteroid and a more severe degree of airway obstruction at baseline were associated with a higher exacerbation rate. The decline in mean FEV_1 was 14.6 mL per year in patients with infrequent exacerbations and 31.5 mL per year in asthmatics, with frequent exacerbations determining a difference between the groups of 16.9 mL per year. Furthermore, the authors found that one severe exacerbation per year was associated with a 30.2 mL greater annual decline in FEV_1. This excess in decline has been proposed to be related to an important remodelling of the airways that occurs during exacerbations [47].

Similarly, O'Byrne *et al.* [48] evaluated the association between asthma exacerbation and lung function decline in patients recently diagnosed with persistent asthma participating in the START (Inhaled steroid treatment as regular therapy in early asthma) study. Their analysis showed that asthmatic patients exacerbating during the study had a more rapid lung function decline if they were not treated with low doses of ICSs [48].

Luskin *et al.* [49] evaluated the relationship between asthma exacerbations and QoL. In this study, a higher level of asthma severity and a higher number of asthma exacerbations were associated with a lower score in the Mini Asthma Quality of Life Questionnaire and hence with a worse QoL [49].

 https://doi.org/10.1183/2312508X.10015516

Pathophysiology of exacerbations

The pathology of exacerbations has not been investigated adequately because of the difficulty in performing invasive manoeuvres in symptomatic patients. Noninvasive assessments have reported further increases of the underlying airway inflammation during exacerbations [11, 50–52]. Enhanced sputum eosinophilia has been documented during exacerbations, particularly in subjects with eosinophilic inflammation in the stable state; however, a substantial proportion of exacerbations are not characterised by high levels of sputum eosinophils [8, 51].

Most of the available data on pathological events that occur in the airways during an asthma attack have been obtained from subjects who died from asthma [53–57]. Studies on fatal or near-fatal asthma have shown an aggravation of the chronic underlying condition, causing pronounced airway wall thickening of all structural components (including smooth muscle and mucus glands), oedema and lumen occlusion by mucus plugs, in a setting of predominantly eosinophilic infiltration [58].

Severe asthma attacks seem to be associated with both eosinophils and neutrophils in the bronchi. Tille-Leblond *et al.* [59] showed that patients with status asthmaticus and severe acute asthma had high eosinophil counts in both sputum and bronchoalveolar lavage samples. Conversely, patients with an associated neutrophilic component usually responded poorly to corticosteroids, and this could aggravate epithelial damage and lead to alterations in epithelial and endothelial permeability associated with acute severe asthma that may contribute to high levels of airway resistance. In addition, they reported that submucosal eosinophilic infiltration was more abundant in cases of slow-onset asthma exacerbations than in sudden-onset asthma, and that submucosal neutrophils were associated mainly with sudden-onset asthma and were less abundant in cases of slow-onset asthma [59].

Airflow obstruction is the primary pathophysiological consequence of these processes. Severe airflow obstruction leads to pulmonary hyperinflation and disordered gas exchanges. The most common derangements in arterial blood gases during asthma attacks are hypoxaemia and hypocapnia. In increasingly severe conditions, alveolar ventilation begins to decrease and $PaCO_2$ starts to normalise, and ultimately hypercapnia and respiratory acidosis can develop [1, 22].

Risk factors for exacerbations

From a clinical perspective, it is important to understand and recognise the risk factors that are able to trigger an acute event, predict future poor outcomes or lead to life-threatening manifestations [1]. Risk factors for asthma exacerbation are those factors that can lead to a deterioration in airway inflammation and/or poor adherence to or inadequate treatment [1].

Identified conditions that increase the risk of exacerbation include exposure to various environmental agents, poor treatment adherence, incorrect use of medication inhalers, smoking, poor asthma symptom control, impaired lung function, comorbidities (*e.g.* rhinosinusitis, obesity) and a history of exacerbations in the previous year [1]. Among environmental agents, viral upper respiratory tract infections, bacteria, allergens, pollens and air pollution are recognised as specific causes of asthma exacerbation [2]. The mechanisms

linking these environmental factors to AEs are addressed in specific chapters of this *Monograph* [60–62].

As mentioned in the previous section, fatal and near-fatal asthma represent the most severe clinical acute presentations of the disease. Near-fatal asthma is described as acute asthma associated with a respiratory arrest or $PaCO_2$ >50 mmHg, with or without altered consciousness requiring mechanical ventilation [11, 63, 64]. The major risk factors for fatal or near-fatal asthma considered by most recent guidelines are listed in table 1 [1].

Manifestations and clinical assessment

Asthma exacerbations can be defined as episodes characterised by a progressive increase that go beyond day-to-day variability in (or development of) asthma symptoms, such as increasing cough with or without sputum production, wheezing, chest tightness, shortness of breath and dyspnoea, usually with a reduction in lung function, which implies loss of control and the need for a change in treatment [1, 65].

Asthma exacerbations can present at any time of an asthmatic patient's life, and sometimes they are the first clinical manifestation of the disease. In general, exacerbations develop after exposure to a triggering agent (*e.g.* viral infection or allergen exposure) or poor adherence to/misuse of inhaler therapy, but in some cases they develop without known exposure to identifiable trigger factors [66]. Asthma exacerbations develop most frequently in severe uncontrolled asthmatic patients; however, even mild and well-controlled patients can experience exacerbations [67, 68]. Usually, exacerbations are acute or subacute in presentation, with the acute phase of the manifestation usually anticipated by a prodromal and progressive deterioration of symptoms that is paralleled by an increase in the need for the use of rescue medications [1]. A minority of patients, however, may poorly perceive symptoms and experience a significant decline in lung function without a perceptible change in symptoms [11, 63].

The most common complaints consist of dyspnoea, cough and wheezing, sometimes as isolated entities, but none is present consistently [69]. Dyspnoea is reported to be absent in

Table 1. Risk factors for fatal or near-fatal asthma

History of near-fatal asthma requiring intubation and mechanical ventilation
Hospitalisation or emergency department visit for asthma in the past year
Previous or current use of a course of oral corticosteroids
Irregular use of inhaled corticosteroids
Not currently using inhaled corticosteroids
Overuse of short-acting β_2-agonists, especially use of more than one canister per month
Poor adherence to medications and/or poor adherence to (or lack of) a written action plan
History of psychiatric disease or psychosocial problems
Food allergy or another atopic disease
Alcohol or drug abuse
Obesity
Learning difficulties
Income problems, employment problems or social isolation
Severe domestic, marital or legal stress
Childhood abuse

Information from [1].

 https://doi.org/10.1183/2312508X.10015516

17–18% of cases and wheezing absent in 5% [69]. Other possible features present are cough, wheezing, impaired mental status, breathlessness, tachypnoea, tachycardia, hyperinflation, accessory muscle use, cyanosis, pulsus paradoxus, diaphoresis and obtundation [1, 22, 69, 70]. These clinical findings are generally accompanied by alterations in lung function tests, namely FEV_1, peak expiratory flow, functional residual capacity and total lung capacity, consistent with airflow obstruction, hyperinflation and increased airflow resistance [69]. In particular, hyperinflation has been addressed as one of the most important contributors to the intensity of breathlessness and to the symptomatic response [69]. However, it has been described that, in some patients, symptoms do not correlate directly with the degree of airflow obstruction, with a consequent possible delay in therapeutic interventions [71, 72].

Asthma exacerbations show extreme variability in terms of the severity of clinical features, ranging from mild to extremely severe with an urgent need for intensive care support, and can ultimately cause death [1]. In recent years, many experts have called for standardisation of the definition of exacerbation and of severity assessment, at both clinical and experimental levels [65, 73].

Reddel *et al.* [65] classified the various levels of severity of exacerbations in an American Thoracic Society/European Respiratory Society document, considering the therapy and the setting required to face the acute event. Thus, exacerbations have been defined as severe if they require the use of a systemic corticosteroid course (or an increase in dosage) for $\geqslant$3 days, or if they require a visit to the emergency department or hospital admission [65]. An exacerbation of moderate degree is clinically identified by a decrease in respiratory function with worsening symptoms that do not respond to bronchodilator rescue therapy, with a greater change in symptoms than daily variability, and which persists for >2 days without requiring hospitalisation or a visit to the emergency department but still requires therapeutic adjustment [65]. The authors considered mild exacerbations to represent episodes of symptom variation outside the normal range of variation for the individual patient, which are difficult to distinguish from a transient loss of asthma control [65].

Recently published international GINA guidelines provide indications for the clinical assessment of asthma exacerbations [1]. In managing asthma exacerbations, key elements are represented by: 1) recognition of asthma exacerbation from differential diagnoses, 2) identification of risk factors for potentially life-threatening asthma, 3) rapid assessment and identification of the severity of the exacerbation and 4) proper management of exacerbations in consideration of their severity. A description of the main differential diagnoses is provided in the following section.

A focused history of the patient (timing, cause and severity of the exacerbation, symptoms of anaphylaxis, risk factors for asthma-related death and current asthma medication) could help clinicians in recognising features of severe asthma attacks and identify predictors of poor outcomes or life-threatening asthma [1].

Symptoms of severe exacerbation include chest tightness, cough, a sensation of air hunger, inability to speak because of laboured breathing, inability to lie down and fatigue. The signs of severe asthma include the use of accessory respiratory muscles, tachypnoea, tachycardia, wheezing or disappearance of wheezing as a sign of severe airflow obstruction, diaphoresis, cyanosis, obtundation and altered mental status, which indicate the requirement for immediate emergency care [1, 22].

The clinical assessment should be aimed at immediate recognition of the potential risk of asthma-related death, such as a history of previous episodes of emergency department visits or hospitalisations, particularly those requiring admission to an ICU or mechanical ventilation [1]. Overuse of reliever β_2-agonists, absence of ICS treatment, or poor adherence to asthma medications and recent withdrawal of systemic corticosteroid treatment are additional major risk factors [1, 22]. Life-threatening situations especially affect patients with a history of near-fatal asthma, and also appear to be more common in males [1].

A severity evaluation should be performed next. The best suggested approach for severity assessment is to perform a multiparametric evaluation, which aims to define the appropriate pharmaceutical interventions to be adopted, and at the same time to define the best clinical context for the patient (*e.g.* ambulatory management, hospital admission). This multiparametric evaluation should consider the following: evaluation of the degree of consciousness of the patient, agitation, posture, use of accessory muscles, respiratory sounds, respiratory rate, heart rate, pulse oximetry and lung function [1, 70]. The latter should include FEV1 whenever available, and in its absence, peak expiratory flow measurement. If predicted values are not available, the percentage of personal best should be used to assess the severity of functional impairment. If available, a blood gas analysis should also be performed, especially in the most severe cases, both to guide oxygen therapy and because a normal or high $PaCO_2$ value has poor prognostic value [1].

International guidelines divide exacerbations into three degrees of severity, mild, moderate and severe, according to such multiparametric evaluation (table 2) [1]. As not all clinical features will necessarily be present at one time, in the presence of clinical aspects belonging to different degrees of severity, the worst should be used to define exacerbation severity.

Standard blood tests, chest radiography and arterial blood gas analyses are not routinely necessary prior to initiating treatment. They should be performed in patients with severe clinical conditions, when arterial oxygen saturation measured by pulse oximetry (SpO_2) is <92% or FEV1 is <30%, when the response to conventional treatment is inadequate and/or to detect concomitant conditions that complicate asthma treatment [1, 70].

Once it has been established that the patient is affected by exacerbated asthma and the degree of severity of the exacerbation has been defined, management will differ depending on the context of the evaluation (*e.g.* primary care or emergency department), the clinical presentation and the clinical response to therapy [1, 70]. Therapeutic management of exacerbations is discussed elsewhere in this *Monograph* [74].

Differential diagnosis

In the management of asthma exacerbations, it is crucial to define and distinguish exacerbations from cases of poor asthma control and from other pathologies that may mimic an exacerbation. Patients facing asthma exacerbations experience an increase in dyspnoea often associated with increased cough, chest tightness and other typical asthma symptoms, such as wheezing, that require an increase in medical therapy. Poor asthma control is defined as an excessive diurnal variability of asthma symptoms and airflow restriction. This is a feature that does not usually occur in asthma exacerbations, which are instead characterised by a progressive worsening of symptoms with a poor response to usual medical therapy [38].

 https://doi.org/10.1183/2312508X.10015516

Table 2. Exacerbation severity assessment

Mild to moderate	Severe	Life-threatening
Not agitated, prefers sitting to lying	Agitated, sits hunched forward	Drowsy, confused, sits hunched forward
Talks in phrases	Talks in words	Not able to talk
HR 100–120 beats·min^{-1}	HR >120 beats·min^{-1}	Hypotension or arrhythmia
RR <30 breaths·min^{-1}, S_{pO_2} ⩾90%	RR >30 breaths·min^{-1}, S_{pO_2} <90%	Inefficient respiratory efforts and/or cyanosis
PEF >50% predicted or personal best	PEF 33–50% predicted or personal best	PEF <33% predicted or personal best
Wheezes at chest auscultation	Wheezes at chest auscultation	Silent chest at auscultation

HR: heart rate; RR: respiratory rate; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; PEF: peak expiratory flow. Information from [1].

Other pathological conditions may simulate bronchial asthma exacerbations and lead to a more challenging management. Among the most common diseases that should be taken into account as differential diagnoses of asthma exacerbations, it is mandatory to consider COPD, vocal cord dysfunction, tracheobronchomalacia, bronchitis, bronchiectasis, CF, tuberculosis, epiglottitis, a foreign body, extrathoracic or intrathoracic tracheal obstruction, cardiogenic pulmonary oedema, noncardiogenic pulmonary oedema, pneumonia, pulmonary embolus, chemical pneumonitis and hyperventilation syndrome [1, 22, 75]. In children, obliterative bronchiolitis, developmental abnormalities of the airways, primary ciliary dyskinesia and other types of non-CF bronchiectasis must also be considered [1, 22, 75]. One challenging differential diagnosis is represented by vocal cord dysfunction, which necessitates direct visualisation of the vocal chords in the course of respiratory symptoms. However, when an asthma diagnosis cannot reliably be ruled out, the symptoms should be treated as asthma and direct visualisation of the vocal chords delayed [69].

Comorbidities

Some comorbid conditions, both allergic and nonallergic (*e.g.* sinusitis, obesity, gastro-oesophageal reflux disease, hormonal changes) can be associated with asthma and may influence susceptibility to develop asthma exacerbations. Interventions aimed at controlling such comorbidities can reduce the risk of exacerbation [1, 76]. In a study by Ivanova *et al.* [45], patients with exacerbations in fact had higher rates of sinusitis, allergy-related diagnosis or medications, otitis media, pneumonia and mental disorders, and a higher Charlson Comorbidity Index score, reflecting a worse QoL and a lower life expectancy.

Conclusion

Asthma is one of the most common chronic respiratory diseases worldwide. The natural history of the disease is punctuated by episodes of worsening in symptoms, termed exacerbations. Asthma exacerbations have a main role in the natural history of the disease, both for their impact on morbidity and mortality and for their economic healthcare burden. They are generally acute or subacute in presentation, and in some cases represent

the initial presentation of bronchial asthma. From a clinical perspective, it is important to understand and recognise the risk factors able to trigger an acute event.

When facing a patient suspected of exacerbated asthma, clinicians must 1) exclude a diagnosis other than asthma, 2) identify potential risks for asthma-related death and 3) assess the clinical severity of the manifestations. Proper asthma management and treatment should aim primarily to prevent and reduce, and possibly eradicate, exacerbation episodes.

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Disclosures: A. Papi has received grants, personal fees and nonfinancial support for board membership, consultancy, lectures, research and travel expenses from the following, outside the submitted work: Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Takeda, Mundipharma and TEVA. He has received grants, personal fees and nonfinancial support for board membership, lectures, research and travel expenses from Pfizer, outside the submitted work. A. Papi has received a grant for research from Sanofi, outside the submitted work. A. Papi has also received personal fees and nonfinancial support for lectures and travel expenses from the following, outside the submitted work: Menarini, Novartis and Zambon.

 https://doi.org/10.1183/2312508X.10015516

COPD: definition, severity and impact of pulmonary exacerbations

Sami O. Simons[1] and John R. Hurst[2]

This chapter reviews approaches to the definitions, severity and impact of exacerbations in COPD. The "clinical diagnosis of exclusion" approach to COPD exacerbation, used in daily practice, contrasts with the symptom-based and healthcare utilisation definitions of exacerbation employed in clinical trials. There are strengths and weaknesses to these different definitions that should be considered when interpreting research. There remains no biomarker of exacerbation, in part because exacerbations are heterogeneous events. What is loosely called "exacerbation severity" is in fact a composite of the severity of the underlying COPD and the severity of the exacerbation insult. There are several scores that may aid the prediction of poor outcomes at exacerbation. Exacerbations affect lung function, health status, the timing of future exacerbations and mortality, and therefore the exacerbation-susceptible "frequent-exacerbator" phenotype experiences a particular burden of disease. Exacerbations also contribute significantly to healthcare expenditure. Prevention and mitigation of exacerbations are therefore key goals of COPD management.

Cite as: Simons SO, Hurst JR. COPD: definition, severity and impact of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 13–24 [https://doi.org/10.1183/2312508X.10015616].

In this chapter, we will consider exacerbations of COPD, focusing on definitions, the assessment of exacerbation severity, and the impact of these events on both patients and healthcare services.

Exacerbation definitions

Exacerbations of COPD are common events with a significant impact on patients and healthcare services [1]. There is no diagnostic test and no biomarker of COPD exacerbation [2]. Therefore, in a patient with known COPD presenting with a deterioration in respiratory health, clinicians use history, examination and investigations to rule in or rule out other diagnoses, and in the absence of a better explanation make a diagnosis of "exacerbation", even when an exacerbation diagnosis was most likely from the start. In

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

daily clinical practice, exacerbation is therefore a clinical diagnosis of exclusion. This is pragmatic, but poorly suited to research. The same approach is used in the 2017 iteration of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document, which defines COPD exacerbation as "an acute worsening of respiratory symptoms that results in additional therapy" [1]. This is also an example of a "healthcare utilisation" (HCU) definition. Conceptually, in HCU definitions, an exacerbation is an event that a patient or clinician decides needs exacerbation treatment. Note that if treatment is not available (*e.g.* in resource-poor settings, or where access to a clinician is limited), a respiratory deterioration would not be classed as an exacerbation. A respiratory deterioration due to another cause that has been misdiagnosed would also be defined as an HCU exacerbation. These are both unsatisfactory consequences of defining an exacerbation by the need for exacerbation treatment.

The alternative to HCU definitions is to measure the change in symptoms and to define an exacerbation when this change crosses a predefined threshold (whether or not the patient receives treatment). This approach has been widely used in research, and when first introduced resulted in the realisation that a large proportion of symptom deteriorations remain untreated [3]. These events have been called "unreported" or "untreated" exacerbations, and they do not appear to be benign. Studies using symptom-based definitions typically report an incidence of exacerbations that is approximately twice as high as with HCU definitions (and this may be advantageous in research, needing fewer patients or shorter follow-up to reach a particular end-point). Typically, unreported exacerbations are milder than reported events [4]. However, the science of measuring symptoms is challenging, both in the collection of (daily) data and in their analysis. Analysis challenges include defining the threshold for exacerbation, "ceiling effects", and how and when to reset the baseline symptom level in the event of incomplete exacerbation recovery.

The "clinical diagnosis of exclusion" approach to the definition of exacerbation raises the question as to what is (and is not) an exacerbation of COPD [5]. The word exacerbate, from the Latin *exacerbare*, means to make something bad even worse. When taken to mean the symptoms of COPD, an exacerbation would include any of the many causes of symptom deterioration that a patient with COPD may experience. However, when taken to refer to COPD itself, an exacerbation would refer only to a deterioration of COPD (rather than a comorbidity). Therefore, other diagnoses, such as cardiac failure, pneumothorax and pulmonary emboli, while potentially meeting symptomatic criteria and indeed HCU criteria if misdiagnosed, are not conceptually exacerbations of COPD (although they are exacerbations of the symptoms of COPD).

This latter issue is particularly complex with pneumonia. Classically, exacerbations are considered to be driven by airway infection, whereas pneumonia represents alveolar infection. These are likely to overlap. Even if a chest radiograph is performed (not routinely recommended during COPD exacerbation [1]), consolidation may be missed if it is early in the course of the disease, or through the insensitivity of the test. The implications of consolidation visible on CT compared with that visible on a chest radiograph are unclear. However, the presence of consolidation on a chest radiograph (which some would call a pneumonic exacerbation, and others pneumonia in a patient with COPD) is important to detect and is associated with a doubling of mortality [6].

A final concern around comorbidity concerns the occurrence of other diagnoses at the same time as COPD exacerbation; for example, exacerbation of COPD in a patient with

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comorbid cardiac failure may result in decompensation of cardiac failure through a variety of mechanisms.

Note that all definitions of exacerbation assume that the diagnosis of COPD is secure. However, in clinical practice, patients may present without robust documentary evidence of poorly reversible airflow obstruction. In this situation, it is pragmatic to manage the situation as an exacerbation of COPD, but every effort must be made to find evidence of the diagnosis, or to arrange follow-up to confirm the COPD diagnosis if this is truly a first presentation. A patient cannot have an exacerbation of COPD if they do not have COPD.

The absence of a diagnostic test to rule in or rule out exacerbation is a challenge. Although it is known that patients typically have a reduction in lung function at the onset of exacerbation, changes in physiology are generally too small to be useful in diagnosis [7], and performing the tests when a patient is unwell can be difficult. Despite much research, there is also no biomarker that can differentiate stable COPD from exacerbation (or indeed exacerbation of COPD from other causes of symptom deterioration). Hurst *et al.* [2] reported on the ability of 36 plasma proteins to differentiate baseline COPD from exacerbation; the best-performing protein was CRP. Others have looked at alternative acute-phase proteins, including serum amyloid A [8] and pneumoproteins such as surfactant protein D [9]. No protein or combination of proteins is able to distinguish stable COPD from exacerbation with sufficient sensitivity and specificity to have clinical utility. An examination of an analogy with myocardial infarction ("exacerbation of ischaemic heart disease") is informative. This also typically presents with changes in symptoms, and was initially confirmed with a physiological test (ECG). This was then supported by progressively more sensitive and specific biomarkers (aspartate transaminase and lactate dehydrogenase, followed by creatine kinase-MB and finally cardiac troponins), such that an abnormal cardiac troponin biomarker is now considered sufficient to diagnose myocardial infarction, even in the absence of symptoms.

In summary, the definition of a COPD exacerbation is complex and remains inadequate. The "clinical diagnosis of exclusion" approach is most useful in practice, whereas research studies must differentiate between HCU and symptom-based approaches, which have respective advantages and disadvantages. Comorbidities may mimic or complicate exacerbation.

Exacerbation severity

In addition to providing a definition of exacerbation as described above, the GOLD document further classifies exacerbations according to severity [1]: patients with a mild exacerbation require treatment with short-acting bronchodilators only, patients with a moderate exacerbation are treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids, and patients with a severe exacerbation require either hospitalisation or a visit to the emergency department.

This classification of "exacerbation severity" is strongly related to the severity of the patient's underlying COPD and indeed multimorbidity: in a patient with severe COPD, only a mild disturbance would appear as a severe insult needing hospital assessment, whereas in a patient with milder disease, such an insult would probably not sufficiently impair functional capacity. Indeed, of all severe exacerbations requiring hospitalisation, 44% occur in patients with very severe COPD, whereas 9% occur in patients with mild COPD [10].

Besides the severity of underlying COPD, other patient factors increase the risk for hospitalisation. These include previous hospitalisations for exacerbations, older age, poorer health status and the presence of multimorbidity [10, 11].

There are other approaches to defining exacerbation severity. These include the severity of the presenting symptoms (mainly dyspnoea), the severity of the physiological change (mainly respiratory insufficiency), the location of care (home, clinic or hospital) and the clinical outcome (mainly mortality) [1, 12, 13].

The major flaw of all "action-driven" definitions of severity is the requirement for treatment intensity or location to classify exacerbation. The initiation of such treatments may vary across different healthcare systems, according to the local availability of healthcare, and therefore lacks generalisability [12, 14]. In addition, although the classification might be "action driven", this classification does not help the clinician in deciding what to do when confronted with a patient with an exacerbation [12]. Ideally, the assessment of exacerbation severity should aid the clinician in treatment decisions and location of care, and should not be used to define the severity retrospectively. A useful tool would identify patients with mild disease in whom improved self-management or management in a healthcare setting other than a hospital might be beneficial. However, it should be able to reliably identify patients with severe disease in whom early escalation of care is warranted (or in whom end-of-life care might be more appropriate).

To aid clinicians, the current GOLD document has formulated several indications for hospitalisation of patients with an exacerbation of COPD [1]. These criteria include a combination of physiological, social and organisational criteria and include: 1) severe symptoms, 2) acute respiratory failure, 3) the onset of new physical signs (*e.g.* cyanosis or peripheral oedema), 4) failure of an exacerbation to respond to initial medical management, 5) the presence of serious comorbidities and 6) insufficient home support. Although they are "common sense", such criteria remain highly subjective. Moreover, the clinical value of these criteria has not been tested under standardised settings. Some researchers have drawn up explicit criteria for hospital admission using a Delphi consensus [15], but follow-up validation studies showed significant methodological shortcomings [16].

Instead of reporting healthcare utilisation, other researchers have used the worsening of the presenting symptoms as a way to classify exacerbation severity [4, 12, 14]. Several clinical scores have been developed to assess the changes in major symptoms, such as dyspnoea, increased sputum volume and purulence. The criteria of Anthonisen *et al.* [17] to classify exacerbations are well known, although they are more relevant to aetiology than severity, predicting the response to antibiotics. Other more recently developed scores to assess symptom severity are the COPD assessment test (CAT) and the exacerbations of chronic pulmonary disease tool (EXACT) scores [4, 14]. Using diary card-reported exacerbations as a reference, both the CAT and EXACT scores have been shown to reflect exacerbation severity, as assessed by a reduction in lung function, exacerbation length and to some extent systemic inflammation [4, 14]. Although both scores appear responsive to patients' symptoms and may thus help in detecting unreported exacerbations, use of these scores for severity assessment in clinical practice remains limited. There is considerable variability in CAT and EXACT scores during an exacerbation, making the definition of cut-off values for severity challenging. In addition, neither score has been validated against clinically important outcomes at exacerbation, such as hospitalisation or mortality.

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An alternative approach has been to construct severity scores. These are intended to identify patients at risk for increased mortality, analogous to current pneumonia and pulmonary embolism severity scores. The BAP-65 (elevated blood urea nitrogen (BUN), altered mental status, pulse >109 beats·min^{-1}, age >65 years) score has been proposed as a COPD-specific prognosis and severity score [18]. Using a large US database of >88 000 subjects admitted with exacerbation of COPD, the authors derived three variables (serum BUN >8.9 mmol·L^{-1}, altered mental status and pulse >109 beats·min^{-1}) that predicted in-hospital mortality (area under the curve (AUC) 0.72) and the need for mechanical ventilation (AUC 0.77) [18]. The BAP-65 score has five distinct classes with mortality ranging from 0.3% (class 1) to 14.1% (class 5). The need for mechanical ventilation ranged from 0.3% (class 1) to 12% (class 5). Because mortality was low in this cohort, the discriminatory value of the five classes was limited; 91% of the total cohort had a low mortality and intubation rate (<2%). The BAP-65 score has not been widely applied in routine clinical practice, probably because of this poor discriminatory capacity and its reliance on administrative data for the diagnosis of exacerbation. Moreover, it has recently been surpassed by two other disease-specific scores.

The IRYSS-COPD (Investigacion en resultados y servicios de salud COPD) study has recently shed light on specific variables related to outcome in COPD patients attending the emergency department [19]. This was a prospective cohort study among 2487 COPD patients with exacerbation attending the emergency department of 16 hospitals in Spain. Using cluster analysis, the researchers could discriminate four distinct phenotypes associated with different outcomes (mortality, ICU admission, need for noninvasive ventilation and other serious complications). Two specific phenotypes clustered around a poor outcome. One cluster could be defined as a "severe respiratory disease" type, with patients characterised by severe obstruction at baseline, but with a low prevalence of comorbidities. These patients tended to have the most altered blood gas values at presentation. The second cluster could be defined as a "systemic COPD" phenotype, with patients clustered by high multimorbidity and severe flow obstruction. Such results again underline that it is the severity of the patient's underlying disease that is the major driving factor behind "exacerbation severity".

The IRYSS-COPD results were further explored in a subsequent study from the same group [20]. Five variables could accurately predict 30-day mortality in patients with an exacerbation attending the emergency department (AUC 0.79). These were baseline dyspnoea (Medical Research Council (MRC) score), the presence of cardiac disease, the use of accessory inspiratory muscles, paradoxical breathing and Glasgow coma scale (GCS) score. Thirty-day mortality in patients with low baseline dyspnoea and the absence of cardiac disease was low (<2%), while mortality was high (55%) in patients with a high baseline dyspnoea (MRC score 5), use of accessory inspiratory muscles or paradoxical breathing upon emergency department arrival and GCS score <15. Patients could be classified into low risk and non-low risk with a specificity of 65% and a sensitivity of 85%.

A second severity score predicting hospital mortality was introduced in 2012 [21]. The researchers collected data from 920 consecutive patients with exacerbation attending the emergency department of two hospitals in the UK. Overall in-hospital mortality in the cohort was 10%. Five variables could accurately stratify patients into different risk groups: dyspnoea, peripheral blood eosinopenia, consolidation on chest radiograph, acidaemia and atrial fibrillation (DECAF). From these variables, a score was constructed: the DECAF score. Mortality in patients with a low DECAF score (0–1) was low (<3.8%). Mortality

increased to 70% in patients with a DECAF score of 5. The DECAF score performed better than the APACHE-II (Acute Physiology and Chronic Health Evaluation II), BAP-65 and CURB-65 (confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, low blood pressure, age ⩾65 years) score for identifying patients at risk for death. These results were validated in a subsequent study in which similar results were reported [22]. The DECAF score can therefore be used to identify low-risk patients (DECAF 0–1) suitable for settings other than hospitals and high-risk patients (DECAF 3–6) at risk of poor outcome. An RCT is currently being undertaken to assess whether low-risk patients can safely be treated at home rather than in hospital (ISRCTN Registry, trial number 29082260).

An alternative score is CODEX (comorbidity, airflow obstruction, dyspnoea and previous severe exacerbations), which has been shown to associate with survival and readmission following hospital admission at 3 months and 1 year [23]. The study was carefully performed, with a separate validation cohort.

There have been only a few studies investigating the added value of biomarkers in the assessment of exacerbation severity. In the ECLIPSE (Evaluation of COPD longitudinally to identify predictive surrogate end-points) study, white blood cell count was the only biomarker associated with hospitalisation [11]. Other studies have shown that higher procalcitonin levels are associated with the need for hospitalisation and the need for noninvasive ventilation [24]. Brain natriuretic peptide (BNP) has been studied as a marker for mortality. Although BNP concentration was significantly associated with the need for intensive care, BNP performed poorly at discriminating in-hospital and short-term mortality [25], and is perhaps better considered a biomarker of cardiovascular multimorbidity rather than a true biomarker of COPD exacerbation severity.

Impact of exacerbations

Lung function decline

Several studies have suggested that exacerbations accelerate the rate of lung function decline in patients with COPD and therefore contribute to variability in disease progression. In the Lung Health Study, COPD patients who were active smokers had an additional 7 mL FEV_1 loss per year after each reported exacerbation [26]. This accelerated rate of FEV_1 decline was not seen in sustained quitters. A second study showed that patients who experience recurrent exacerbations have a faster rate of lung function decline, with an annual excess of 8 mL [27]. This latter study was relatively small, consisting only of 161 patients attending a single outpatient clinic. Larger studies, including data from the TORCH (Towards a revolution in COPD health) and ECLIPSE trials, have since shown a moderate effect of exacerbations on annual FEV_1 decline [28, 29]. In the ECLIPSE trial, prior reported exacerbations did not have an effect on FEV_1 decline. Exacerbations captured during the follow-up period did have a significant but small additional effect of 2 mL FEV_1 decline per year [29]. In the latter study, smoking, bronchodilator reversibility and emphysema had a greater effect on the annual rate of FEV_1 decline.

The rate of disease progression seems particularly aggravated in patients with mild or early disease. In a recent paper from the COPDGene investigators where COPD patients were followed for 5 years and exacerbations were recorded every 6 months, exacerbations had a significant effect on lung function decline [30]. In patients with moderate to severe COPD,

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each moderate exacerbation resulted in an excess decline of 8–10 mL per year, similar to results from the Lung Health Study [26] and the London Cohort Study [27]. In contrast, in patients with mild COPD, each moderate exacerbation was associated with an additional 23 mL decline in FEV1 per year. Exacerbations requiring hospitalisation had an even more detrimental effect, with an additional decline of 20 mL per year in moderate to severe COPD patients, and an additional 87 mL per year in patients with mild COPD [30]. These data provide information in greater detail on the effect of exacerbations on disease progression in COPD and suggest that patients with mild COPD and frequent exacerbations may be particularly at risk for progressing to more advanced COPD.

Timing of the next event

Exacerbations are not random events. We will describe in a later section that there are a group of patients who appear more susceptible to developing exacerbations, known as "frequent exacerbators". There are also high-risk time periods for exacerbation. Perhaps the most obvious effect on timing of exacerbation is seasonality, with exacerbations typically being more frequent at times when there is higher circulation of the respiratory viruses that drive most of these events.

Also relevant with regard to the impact of an exacerbation is the effect that a first exacerbation has on the timing of subsequent events. Data in support of this come from diverse studies, in which we must make a distinction between a concept that might be called relapse (a further deterioration in symptoms within one exacerbation as it recovers and before complete recovery) and "recurrence" (the occurrence of a completely new second event in the period following complete recovery from a first) (figure 1).

In an observational study, it has been reported that, in the 2-week period following complete recovery of exacerbation, there is a 27% risk of recurrence, which is 20% higher than would be expected if exacerbations were occurring randomly [31]. In an RCT of outpatient prednisone treatment for exacerbations, which did not distinguish between relapse and recurrence, 27% of patients randomised to prednisone required a repeat emergency room visit within 30 days [32].

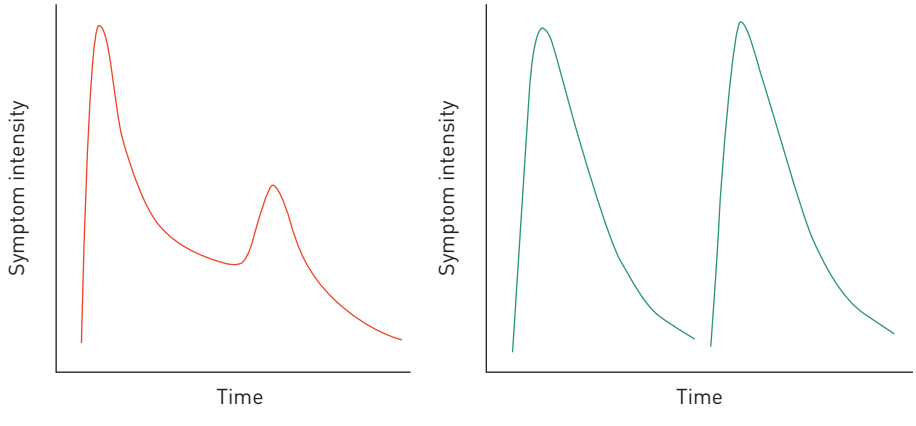

Figure 1. Exacerbation relapse (red) and recurrence (green).

Such data have particular implications for hospitalised exacerbations. Recent data from the 2014 UK National COPD Audit demonstrated that 24% of patients surviving to discharge were readmitted within 30 days, and 43% were readmitted within 90 days [6].

Health status

An exacerbation of COPD has a considerable impact on the health status of people living with COPD [14, 33]. In the London COPD Cohort, for example, patients were followed prospectively, and exacerbations were recorded using diary cards together with the CAT score as a measurement of health status [14]. The CAT score rose significantly, by 5 points on average, at the onset of an exacerbation and returned to baseline after a median of 11 days with treatment. Other studies have shown similar results, with a rapid improvement over 2–4 weeks and then a slower improvement in health status by 6 months if no relapse is seen [33].

Patients who have recurrent exacerbations seem to have a poorer health status. Patients with frequent exacerbations have a worse health status compared with COPD patients who have fewer exacerbations [34]. Prospective cohort studies have shown that, after an initial exacerbation, patients with a relapse have a lower health status after 6 months and do not return to their baseline health status [33, 35].

In addition to the effect of reported exacerbations, unreported events, as discussed earlier, also have an impact on the health status of patients with COPD [3]. In a further cohort study in which COPD patients were followed for 1 year, unreported exacerbations were associated with a significant impact on health status [36], suggesting that unreported events have a long-term negative effect on QoL. Increased recognition of these unreported events and providing adequate treatment might therefore have a beneficial effect on health status and also improve the rate of future exacerbations. In the ECLIPSE cohort, COPD patients who had a stable or improved health status after 1 year had a lower rate of exacerbations in subsequent follow-up period [37].

Mortality

Patients with exacerbation of COPD have an increased risk of death, especially when hospitalised. Various studies have shown that the in-hospital mortality varies between 11% and 24% [38]. Risk factors for in-hospital mortality have been studied extensively. Patients at risk of death often have more severe symptoms, more cardiac comorbidities and more significantly altered physiology at presentation [19–21]. On the basis of these factors, several risk scores for predicting in-hospital mortality have been developed that can accurately detect both low- and high-risk patients, as discussed in a previous section.

The risk of death remains elevated, even after discharge. One-year mortality after hospitalisation for an exacerbation ranges from 22% to 43%, depending on the severity of the underlying COPD [38]. Risk factors for mortality after hospitalisation are higher age, low body mass index, low serum albumin, high P_aCO_2, low P_aO_2/inspiratory oxygen fraction (F_IO_2), comorbidity and functional status [39]. Besides these factors, exacerbations have an independent effect on mortality. In a cohort study of 304 stable male COPD patients who were followed for 5 years, exacerbations increased mortality. Those patients hospitalised for exacerbation had a higher risk of death (hazard ratio (HR) 2.94, 95% CI 1.82–4.72) in the

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subsequent years compared with patients without any exacerbations [39]. The 1-year and 5-year mortality in patients admitted to hospital with exacerbation was 11.6% and 55.2%, respectively. The risk of death in patients attending the emergency department, but who were not subsequently admitted, did not differ significantly from that of patients without exacerbations. Patients with frequent hospitalisations and patients with readmissions were at greatest risk of death. Compared with patients without exacerbations, patients with more than three severe exacerbations and patients with readmissions both had a higher risk of death (HR 4.30, 95% CI 2.62–7.02, and HR 4.31, 95% CI 2.70–6.88, respectively) after 5 years [39]. In part, this may reflect the elevated cardiac risk that has been noted at exacerbation of COPD [40, 41].

There seems to an accelerating effect of subsequent exacerbations on the risk of death. In an elegant study by Suissa *et al.* [42], patients with COPD were followed after a first exacerbation requiring hospitalisation. The median time to death after the first hospitalisation was 3.6 years. The risk of death remained stable between a first and second hospitalisation, but after the second hospitalisation, the likelihood of death increased with each subsequent hospitalisation (figure 2).

The "frequent exacerbator"

Although, in general, exacerbations become more frequent as the spirometric severity of disease increases, the best predictor of future exacerbations is a history of past events [34], and patients are able to reliably self-report their exacerbation history [43]. This has led to the concept of a "frequent-exacerbator" phenotype, typically defined as two or more exacerbations in the past 12 months requiring treatment with antibiotics and/or systemic corticosteroids. People with COPD susceptible to frequent exacerbations have poorer outcomes, including worse health status [3], higher mortality [39] and, although the effect is not large, a faster decline in lung function [27]. Therefore, in addition to "high-risk" time periods for exacerbation, there are high-risk patients, and frequent exacerbators are a group in whom it is particularly important to target exacerbation reduction interventions.

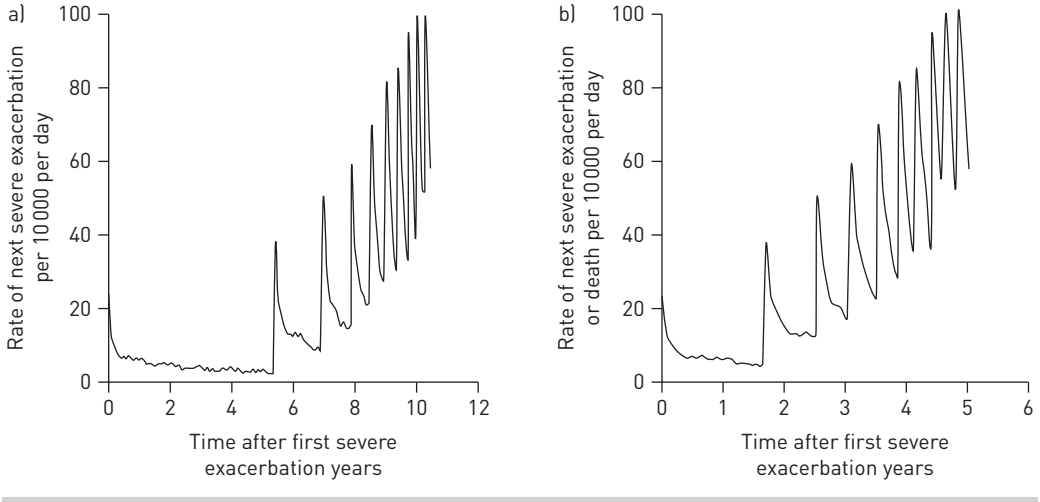

Figure 2. a) Rate of severe exacerbations and b) rate of severe exacerbation or death after each successive hospitalised COPD exacerbation. Reproduced from [42] with permission.

The reasons why some patients experience more exacerbations than others remain incompletely explained. There are a number of plausible biological mechanisms for which evidence is mounting, including altered innate and adaptive immune function [44, 45], altered bacterial colonisation (although this is difficult to define in the era of the microbiome) [46] and gastro-oesophageal reflux [34].

Although generally stable when defined as zero or two or more exacerbations per year, particularly over 2 or more years [34], patients experiencing one exacerbation in the previous year have a more unpredictable future course [34], and the characteristics of patients who change exacerbation frequency status have been explored, but without conclusive results [47]. It should be noted that the proportion of frequent-exacerbator patients depends on the nature of the population, and there are few data examining exacerbation frequency in COPD in an unselected representative population. A large UK population database suggested a prevalence of 28%, with more severe dyspnoea, lower lung function, cardiovascular comorbidity, depression, osteoporosis and female sex associating with exacerbation risk [48].

Airway inflammation

Although now removed from the GOLD definition, COPD has previously been defined by, and is still characterised as, a condition associated with abnormal airway inflammation [1], and, in general, exacerbations are associated with further increases in airway [49] and systemic [2] inflammation. There is some evidence to suggest that frequent exacerbators may have greater airway inflammation in the stable state [50]. There is also evidence to suggest that nonrecovery of symptoms is associated with persisting inflammation, and that persisting systemic inflammation, even when an exacerbation has recovered, is associated with a shorter time to the next exacerbation [51]. The role of ongoing inflammation in the airway and systemic compartments, how this might be modulated with therapy and whether this approach results in improved clinical outcomes remain unanswered questions.

Cost/healthcare impact

Much of the healthcare costs of COPD relate to exacerbations. In 2010, the National Institute for Health and Care Excellence (NICE) in the UK estimated that the total annual direct cost of COPD to the National Health Service was over GBP800 million, equating to GBP1.3 million per 100 000 people [52], and in the USA this was estimated at USD50 billion [53]. It therefore follows that even a small decrease in exacerbation frequency or "severity" (hospitalisation) can have a significant beneficial impact on healthcare resources, and that a smaller group of frequent-exacerbator patients with more severe disease are disproportionately responsible for much of the costs in COPD.

Conclusion

We have reviewed approaches to the definition, severity and impact of COPD exacerbations. Exacerbations affect lung function, health status, the timing of future exacerbations and mortality, and therefore the exacerbation-susceptible "frequent-exacerbator" phenotype experiences a particular burden of disease. Exacerbations also contribute significantly to healthcare expenditure. Prevention and mitigation of exacerbations therefore remain the keys and incompletely mitigated goals of COPD management.

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Disclosures: J.R. Hurst has received personal fees and nonfinancial support, outside the submitted work, for educational meetings and advisory boards, and support to attend conferences from the following pharmaceutical companies: AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, GSK, Grifols, Novartis, Pfizer and Takeda.

 https://doi.org/10.1183/2312508X.10015616

Cystic fibrosis: definition, severity and impact of pulmonary exacerbations

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Pulmonary exacerbations are common events in patients with CF lung disease. Although we lack a consensus definition, they are generally defined as worsening of the daily respiratory and systemic symptoms, often with an acute drop in pulmonary function. For a myriad of reasons, described here, the current best definition of a pulmonary exacerbation is the physician's decision to treat for that indication. The problem with this definition is demonstrated by the variability among clinicians. Issues with other attempts at a definition are also reviewed here. Similarly, there are hurdles to establishing the severity of an exacerbation, as treatment decisions such as hospitalisation are influenced by factors other than worse illness. Exacerbations are associated with multiple adverse outcomes, including loss of lung function, high financial burden and even mortality. Understanding the causes of exacerbations and development of therapies to prevent them are of utmost importance.

Cite as: Flume PA, VanDevanter DR. Cystic fibrosis: definition, severity and impact of pulmonary exacerbations. *In:* Burgel PR, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 25–37 [https://doi.org/10.1183/2312508X.10015716].

Lung disease begins early in the patient with CF [1]. Abnormalities in the airway surface liquid and mucociliary clearance render the airways vulnerable to chronic infection and excessive inflammation [2]. These account for chronic respiratory signs and symptoms (*e.g.* daily cough) and progressive loss of lung function. Intermittent episodes where respiratory signs and symptoms worsen are commonly referred to as pulmonary exacerbations [3]. For some individuals, daily respiratory symptoms appear relatively stable, and exacerbations may be considered acute in onset, while for others, symptoms may be steadily progressive and their "exacerbations" are more accurately characterised as recognition that their condition has truly worsened. In either case, these events are generally managed by an increased intensity of treatment, including chest physiotherapy, nutritional supplementation and administration of antibiotics, either systemically or topically, and sometimes both [3].

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

Pulmonary exacerbations are common and frequent events, beginning in infancy in CF patients. Between 2003 and 2005, North American CF clinicians identified and treated an average of 1.2–1.3 exacerbations per year using antibiotics across all patient ages [4]. Approximately 80% of CF subjects <6 years of age who were enrolled in a randomised 48-week prospective study of inhaled hypertonic saline experienced an exacerbation (defined as treatment with oral, inhaled or intravenous antibiotics for one or more pre-specified signs and symptoms), with an incidence rate of 2.3 exacerbation events per patient-year [5]. In 2014, >17 000 pulmonary exacerbation events were diagnosed and treated with *i.v.* antibiotics among 34.9% (>10 000) of US patients followed in the CF Foundation Patient Registry [6]. Exacerbations are clinically important, as they are associated with considerable morbidity and cost [7–10], yet we still have a poor understanding of their aetiologies and their optimal management [11].

This chapter will address what we know about the definition of these events and explore their impact on the overall health of the patient. Treatment of exacerbations is addressed in another chapter in this *Monograph* [12].

Defining a CF exacerbation

There is no broadly accepted consensus definition of a CF exacerbation, despite pulmonary exacerbations being common events [13]. In general, an exacerbation has a clinical definition in which there is acute worsening of signs (*e.g.* haemoptysis) and symptoms (*e.g.* increased cough and sputum production), often accompanied by an acute decrease in lung function. Yet there is considerable variation in clinician determination of an exacerbation; physician interpretations of clinical vignettes in which clinical factors and options for treatment were varied demonstrated no absolute consensus for any scenario, and there was variability between and within care centres, and even a lack of a consistent approach by individual providers [14, 15]. A consistent definition is desirable, as it is likely to improve clinical care of patients by standardising the approach to care, as well as educating future CF caregivers; it would also be useful for clinical research by providing consistency for comparison of studies and assuring commonality of subjects enrolled in studies of exacerbations (*e.g.* treatment of exacerbations), as well as for determining relevant clinical end-points for studies of chronic therapies.

There are both similarities and notable differences in exacerbation definitions suggested or described for other pulmonary conditions, including COPD, bronchiectasis (due to other causes) and interstitial lung diseases (ILD). Exacerbation in the latter has been described as sudden disease acceleration or an acute injury in the setting of diseased lung [16, 17]. Similar to CF, there is no consensus ILD exacerbation definition, but proposed criteria include ILD diagnosis with unexplained acute worsening of dyspnoea and new bilateral ground-glass abnormality and/or consolidation on HRCT, but with the exclusion of other aetiologies, including infection, heart failure, pulmonary embolism or an identifiable cause of acute lung injury [17]. Thus, acute changes must be attributed to the underlying disease process (as opposed to infection), which is distinct from the situation in CF. The COPD pulmonary exacerbation definition is an acute, sustained worsening of the patient's symptoms beyond the day-to-day variability [18]. A patient-reported outcome instrument was developed to evaluate exacerbation outcomes in COPD clinical trials [18], but has not found its way to routine use in the clinic. COPD exacerbation definitions generally allow for multiple aetiologies that include infection. Non-CF bronchiectasis exacerbations seem to

 https://doi.org/10.1183/2312508X.10015716

be most similar to what has been described for CF, as CF patients have bronchiectasis, and chronic infection is typically present in both CF and non-CF bronchiectasis. A recent consensus conference definition consists of the presence of three or more key symptoms for at least 48 h, as well as a clinician's decision to treat, but the treatment does not require antibiotics [19].

The literature on CF pulmonary exacerbation typically considers exacerbation diagnosis either in the context of an inclusion criterion for a treatment study or as a clinical efficacy end-point for a chronic intervention. For the former, the definition of exacerbation has been based solely on a physician's decision to treat with antibiotics [20–23], with occasional descriptions of clinical features such as "deterioration of their general condition, manifested by general ill health, decreased exercise tolerance, increased cough and volume of purulent sputum" [22]. However, there were also statements of what was not observed, such as "the usual features of infection such as pyrexia and increases in white cell count […] may not be present in an acute on chronic exacerbation […] it may also be very difficult to see new changes on chest radiograph" [23], essentially acknowledging that there could be variation in patient presentation. More recently, lists of respiratory signs and symptoms present at the decision to treat have been adopted. Blumer *et al.* [24] required the presence of at least five out of 10 possible signs and symptoms to enrol in a comparative treatment trial, and Dovey *et al.* [25] required hospitalisation with at least three out of a set of 11 criteria provided in the Clinical Practice Guidelines of the Cystic Fibrosis Foundation [26] for enrolment in a subsequent trial.

In contrast to these exacerbation treatment studies, studies of chronic CF therapies employing a reduction in exacerbation rate or risk as an efficacy end-point have commonly included a requirement that patients present with a threshold number of respiratory signs and/or symptoms in addition to the physician's decision to treat with antibiotics for events to be designated as exacerbations [27–32]. Although not truly "objective", these prospective definitions assured investigators of a respiratory basis for antibiotic intervention. However, not all analyses of chronic therapies have employed additional criteria beyond the physician's decision to treat to study the effects on exacerbation incidence [29, 33–35]. Published exacerbation definition components are shown in table 1.

Researchers have retrospectively studied exacerbation treatment data from clinical trials and CF patient registries, and quantified the coincidence of respiratory signs and symptoms to generate more "objective" definitions that they have used to estimate the incidence of and outcomes for untreated exacerbations [36–38]. These retrospective definitions share many components of prospective clinical trial definitions (table 1). Interestingly, although these definitions are reasonably good at identifying signs and symptoms that are likely to be present when a patient is treated for exacerbation, they are not particularly good at predicting treatment for exacerbation [37].

Although there are many similarities among the exacerbation definitions found in table 1, they differ in their sensitivity, and there are some key observations. First, these definitions require identification of a change in a given criterion from a patient's stable condition, which is largely a subjective undertaking. Changes in four specific parameters (increased cough, change in purulence or volume of sputum, lung function decline and weight loss) are common to all of these definitions, while others (changes in chest examination, absenteeism, exercise tolerance, chest radiograph and temperature) are found in a majority, and some (increased dyspnoea, sinus pain, decreased oxygen saturation and neutrophilia)

Table 1. Published exacerbation definitions showing the sign and symptom change criteria

Sign or symptom change criterion	First author [ref.]						
	Ramsey [27]	Fuchs [28]	CF Foundation [26]	Rosenfeld [36]	Rabin [37]	Blumer [24]	Kraynack [38]
Cough	✓	✓	✓	✓	✓	✓	✓
Sputum	✓	✓	✓	✓	✓	✓	✓
Lung function	✓	✓	✓	✓	✓	✓	✓
Weight	✓	✓	✓	✓	✓	✓	✓
Chest examination		✓	✓	✓	✓	✓	✓
Absenteeism	✓		✓	✓		✓	✓
Exercise tolerance			✓	✓		✓	✓
Chest radiograph		✓	✓			✓	✓
Temperature	✓	✓	✓				✓
Haemoptysis		✓			✓		✓
Dyspnoea		✓				✓	✓
Fatigue/malaise		✓				✓	✓
Tachypnoea	✓		✓			✓	
Sinus pain	✓	✓					
$Sa0_2$			✓				✓
Sinus discharge		✓					
Neutrophilia	✓						
Diagnostic formula[#]	2/7+1/3	4/12+*i.v.* antibiotics	3/11	Score	3/4	5/10	Score

[#]: methodology for diagnosis. Reproduced and modified from [39] with permission.

are only occasionally included. As noted, two of the definitions in table 1 require that treatment, either an increase in routine therapy or the addition of an antibiotic, be administered in order for a definition of exacerbation to be met [25–28]. Finally, these are all comprised of clinician-reported criteria; none of the definitions includes patient-reported components, despite recognition that changes in patient perception of feeling and function are highly relevant to the diagnosis [40, 41]. Recently, an instrument capturing patient-reported exacerbation symptoms, the CF Respiratory Symptom Diary and Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) [42, 43], has been employed prospectively to identify "early" exacerbations [44], as well as the response to exacerbation treatment [45]. It remains to be seen whether CFRSD-CRISS will become a practical tool for incorporating patient-reported criteria into CF exacerbation definitions.

Investigators have experimented with an entirely objective prospective exacerbation definition divorced from the clinician's decision to treat, most frequently defining exacerbation as changes in four or more Fuchs criteria (table 1) [29, 46, 47]. As was observed in an earlier epidemiological analysis [37], events defined in this manner were not uniformly treated with antibiotics by investigators. For example, during a 48-week hypertonic saline study, 84% of placebo subjects met the exacerbation definition of four or more Fuchs criteria, but only 38% were reportedly treated with *i.v.* antibiotics when these symptoms were present [29]. Similarly, only 55% of patients meeting the four or more Fuchs criteria during an 8-week inhaled levofloxacin study were treated with any antibiotics

 https://doi.org/10.1183/2312508X.10015716

for exacerbation when presenting with at least four Fuchs criteria [47, 48]. Furthermore, there were no substantial differences in the particular criteria that resulted in antibiotic treatment *versus* those that did not [48]. These observations suggest that a much more sophisticated process of choosing sign and symptom criteria accompanied by clinical validation will be required if a purely objective exacerbation definition is to be realised.

Since the physician's decision to treat with antibiotics is a common component of most exacerbation definitions, analyses of patient registry data have often used this (*i.e.* antibiotic treatment) as a surrogate indicator of exacerbation [4, 37, 49–54]. This pragmatic approach recognises that CF patient registries typically do not capture respiratory signs and symptoms, but do track antibiotic administration, as well as the clinician's diagnosis of exacerbation. There are some notable limitations to this approach, and the reader is cautioned when interpreting these data. First, this approach leaves the diagnosis of exacerbation to the treating clinician, despite recognition of the substantial variability that can exist between clinicians with respect to thresholds for antibiotic intervention [13, 15, 38, 55]. Second, this approach (by definition) assumes that there are no untreated exacerbations, yet it has been shown that substantial numbers of patients with apparently similar respiratory sign and symptom presentations go untreated in the CF population [37]. Finally, it appears that thresholds of antibiotics used to treat exacerbations have evolved over recent decades [56], meaning that a given patient's history and clinical presentation may now be more or less likely to be treated with antibiotics than might previously have been the case.

Not all antibiotic usage is acute and related to exacerbation treatment in CF management; increasingly, antibiotics are administered as prophylactic agents [57, 58] or as part of chronic bacterial suppression regimens [46, 59–62]. A common approach to avoid mistaking these "other" antibiotic uses as exacerbation treatments in epidemiological analyses is to limit analyses to treatments involving *i.v.* antibiotics only [49, 51, 53, 54, 63–65]. This approach increases the probability that a treatment event was also considered an exacerbation by the treating clinician, but practices remain in which scheduled *i.v.* antibiotic treatments comprise chronic suppression strategies [55, 59]. Perhaps more importantly, this approach fails to capture the substantial number of exacerbations treated with other systemic (*i.e.* oral) and/or inhaled antibiotics [4, 66, 67]. The decision as to whether to use *i.v.* antibiotics depends on a number of factors, including an assessment of exacerbation severity, where mild exacerbations (with fewer or less pronounced clinical symptoms) are often treated on an outpatient basis with oral or inhaled antibiotics, and more severe exacerbations often result in admission to the hospital and administration of *i.v.* antibiotics [11, 56]. A patient's age, stage of lung disease, the pathogens targeted for treatment with the antibiotics (*e.g. Pseudomonas aeruginosa* has few oral options, but *Staphylococcus aureus* has several), the availability of home resources and previous experience with the patient may all factor into the decision as to which antibiotic regimen to use [4, 52].

Difficulty in deriving an acceptable prospective exacerbation definition probably has multiple origins, many involving factors related to clinical presentation. For instance, age-related differences in clinical presentation affect the relevance of some criteria: preschool children with CF may wheeze rather than cough, may not produce sputum and are unlikely to perform spirometry effectively [68]. Younger patients may also have new pulmonary or constitutional symptoms, or new physical signs (*e.g.* crackles on lung examination) that are perhaps less well appreciated in older patients [68]. Observations that signs and symptoms most commonly associated with a physician's diagnosis and treatment

of exacerbation differ by patient age illustrate this problem [37]. Furthermore, many of the criteria listed in table 1 represent a change in status from a perceived (often unrecorded) baseline, making it problematic for a new clinician to have the same appreciation for status change as a clinician with a history of managing a patient. In addition, none of the criteria lists in table 1 includes psychosocial factors that probably influence diagnosis. Again, clinician history with a patient is extremely important, as he or she may be sensitised to certain clinical presentations unique to that patient, with some criteria changes possibly carrying greater weight during exacerbation diagnosis. We must also consider the patient's participation in the diagnosis, potentially either exaggerating or minimising symptoms, with full knowledge of what is likely to follow. Indeed, outpatient or inpatient treatment with antibiotics is the product of a negotiation between the patient/family and physicians. Of course, patients have the option of refusing antibiotic treatment, and thus an absence of treatment does not necessarily reflect the opinion of the physician with respect to exacerbation diagnosis. The observation that history of exacerbation is the strongest reported risk factor for future exacerbation is probably related to the longitudinal relationships between patients, families and care providers [54].

Finally, multiple exacerbation aetiologies have been proposed, ranging from viral infection [69–71], a change in the bacterial community [72, 73], environmental effects (*e.g.* pollution) [74, 75] and even poor adherence to therapies [68, 76], all of which may have distinct presentations in terms of clinical onset and relative severity. There are also other pulmonary complications, notably pneumothorax and massive haemoptysis, which might be treated similarly [77], but they do not fit within the general scope of an exacerbation definition.

Severity of an exacerbation

Characterisation of the "severity" of an exacerbation, which would be of great interest to clinicians and epidemiologists, has not been thoroughly explored. Traditionally, events resulting in hospital admission and/or *i.v.* antibiotic treatment have been considered to be more severe when compared with those treated with outpatient oral and/or inhaled antibiotics, but this distinction may be problematic. This is because factors other than severity of clinical presentation may lead to the recommendation for *i.v.* antibiotic treatment and/or hospital admission, including reimbursement requirements, the bacterial species being targeted, drug allergies or intolerances, and gastrointestinal contraindications, which might be better described as pragmatic rather than severity factors. What is less problematic is assigning greater severity to those events associated with greater morbidity to the patient, such as the acute need for supplemental oxygen, hypercapnic respiratory failure, severe electrolyte disturbance, malnutrition or substantially reduced QoL. Importantly, unlike antibiotic route and treatment location, these are not factors that are systematically collected in association with diagnosis and treatment of exacerbation, and so are not readily available to characterise exacerbation severity. Although *i.v.* antibiotic-treated CF exacerbations have been associated with increased mortality risk [78–80], a lack of available data has precluded more granular assessments of associations of specific clinical presentations at exacerbation and survival. Clearly, this would be an area of great interest to investigators if these data were available.

Many, but not all, patients diagnosed with exacerbation will have experienced a drop in their lung function relative to a previously stable value (*i.e.* their "baseline"), and the extent

 https://doi.org/10.1183/2312508X.10015716

of decline might be considered an indication of exacerbation severity. Although a drop in lung function is a common criterion associated with antibiotic treatment [37], acute FEV1 drops often go untreated [81]. When North American CF care programmes with ⩾50 patients were stratified by quartiles based on the medians of each patient's best FEV1 for separate age groups (<6, 6–12, 13–17 and 18+ years of age), it was observed that only ∼50% of patients with relative FEV1 drops of ⩾15% were treated with antibiotics at the highest quartile sites *versus* <45% at the other sites (p<0.001) [81]. This lack of treatment of acute lung function drops is compounded by a significantly higher frequency of these events in lower quartile sites, ranging from ∼45% of patients at the lowest quartile sites to 40% of patients at the highest quartile sites (R^2=0.993; p<0.001) [81]. The observation that the majority of FEV1 drops of ⩾15% went untreated in this population is at odds with the proposition that magnitude of FEV1 drop alone is a useful indicator of exacerbation severity. In addition, a recent observational study found that ∼20% of patients admitted to the hospital for *i.v.* treatment of an exacerbation (which we might consider severe based on antibiotic administration route) had better lung function at hospital admission than any of their measures recorded in the prior 6 months, indicating that either our methodology for measuring lung function drop is inadequate or that lung function drop has limitations as a measure of exacerbation severity [80]. Indeed, although lung function recovery appears to be a primary goal for a majority of treating US physicians, patients appear to be much more interested in symptom resolution [82]. Finally, although it may be appealing to consider a patient's clinical presentation and treatment as a surrogate for the relative severity of an exacerbation, it might be more useful to include the extent of their recovery following treatment; if an individual loses 5% of lung function that is never recovered *versus* 15% that is completely recovered, which was the more severe event? Therefore, for the moment, it may be best to describe the severity of events based on outcomes (*e.g.* lack of recovery of lung function or survival), and then perhaps factors predicting differing outcomes can be identified at the time of diagnosis.

Haemoptysis is a relatively common sign and is often treated as a manifestation of an exacerbation [77], but in and of itself is probably not a useful indicator of exacerbation severity. This is because, in most instances, a diagnosis of haemoptysis is associated with only scant to small amounts of blood loss, and there can be instances where patients experience haemoptysis in the absence of other criteria typically associated with pulmonary exacerbations [83]. Unfortunately, CF patient registries track massive haemoptysis only, so the natural history and incidence rate of milder haemoptysis is less well characterised. However, massive bleeding (>250 mL in 24 h or >100 mL·day^{-1} for 4 days) is certainly an important complication, and exacerbations with coincident massive haemoptysis should be considered "severe" events [77].

Given that a heightened inflammatory response has been proposed as a "hallmark" of pulmonary exacerbation [13], it follows that measurement of sputum or serum biomarkers of inflammation might assist in defining an exacerbation and/or perhaps even severity at diagnosis, but to date this has not been the case. This has probably been due to the lack of consensus on how exacerbation severity might be clinically characterised, which has limited researchers' ability to suggest a correlation with inflammatory marker titres. Beyond the challenge of the lack of "baseline" inflammatory marker measures for comparison during clinical presentation for exacerbation, studies of relationships between lung function recovery and systemic and local inflammatory marker changes during and after exacerbation treatment have reported somewhat contradictory results [84–87]. Recent reports that systemic CRP concentrations are associated with increased risk of subsequent

exacerbation support the role of inflammation in exacerbation [87–89], but to date there are no firm data suggesting a link between CRP or other inflammatory marker concentrations and exacerbation severity.

Impact of an exacerbation

There are numerous studies describing the adverse outcomes associated with pulmonary exacerbations, but it is important to note that these analyses are derived from events that have been recognised and treated by clinicians. One can only speculate as to the number of exacerbations that go undiagnosed and the outcomes associated with them. Perhaps most dramatically, (treated) pulmonary exacerbations have been associated with decreased survival [78–80, 89]. An increase in 2-year mortality has been associated with exacerbation-related hospitalisations, particularly for individuals with two or more hospitalisations in a given year [79]. Mortality rates are higher for patients receiving exacerbation treatment in the ICU [90]. Beyond these sobering observations of increased mortality risk, exacerbations are associated with a myriad of adverse impacts on the lives of CF patients and their families. Since increases in signs and symptoms are commonly the means by which exacerbations are recognised (table 1), it may not be surprising that they have been associated with reduced patient QoL [9, 91].

As noted in the previous section, exacerbations are often associated with an acute drop in lung function [37]. Although lung function recovery is a common goal of clinicians when administering antibiotics [82] and antibiotic treatment of exacerbation has been shown to significantly improve lung function [92], treatment with antibiotics fails to return most patients to their best lung function values recorded in the prior year (*i.e.* their pre-exacerbation "baseline") [67, 93]. In separate retrospective studies, 57.7% of patients receiving *i.v.* antibiotic treatments for exacerbation failed to return to at least their baseline FEV1 values [93], a fate shared by 55.6% of patients treated with oral antibiotics [67]. In a consistent parallel observation, the rate at which an individual's FEV1 declines has been associated with their pulmonary exacerbation frequency [63, 94]. It is not clear why treatment of exacerbation does not consistently result in complete recovery of lost lung function. Although it is tempting to suggest that poor health outcomes are not the result of inadequate or misguided exacerbation treatment, there is some evidence to the contrary. We know that patients do benefit from intervention, as it has been shown that young children who meet the clinical criteria most commonly associated with a pulmonary exacerbation, but who are not treated, are known to have worse lung function later in life [95]. However, it has also been observed that patients treated for shorter durations with *i.v.* antibiotics (*i.e.* <10 days) or who are not admitted to the hospital have an almost 2-fold greater risk of readmission to the hospital within 30 days after treatment than their peers treated for longer periods or partially in the hospital [65]. Thus, we must conclude that poor exacerbation treatment probably accounts for some proportion of poor outcomes and future exacerbations.

Exacerbations have also been associated with other complications that may not commonly be associated with exacerbation diagnosis, such as increased pain [91], although elevated pain levels and corresponding decreased QoL are not limited to exacerbations in persons with CF [96]. Exacerbations have also been associated with altered glucose homeostasis, such as hyperglycaemia in patients with established CF-related diabetes [97] and an abnormal oral glucose tolerance test in others [98]. Exacerbating patients experience

 https://doi.org/10.1183/2312508X.10015716

catabolism, a negative nitrogen balance and loss of fat-free mass [99], as well as reduced muscle strength [100]. Increases in osteoclasts may contribute to bone loss and increased osteoporosis risk [101, 102], hypotheses supported by observations of altered bone metabolism during exacerbation [102, 103].

Exacerbations typically result in treatments that increase the overall cost of care [8, 10], but that also increase school and work absenteeism, which can in turn lead to additional financial hardships, and the treatment itself may be associated with morbidity, ranging from the minor annoyance of gastrointestinal disturbances to more severe complications of drug–drug interactions and toxicities. Many antibiotics commonly used to treat exacerbations are nephrotoxic, and aminoglycosides, a common class included in *i.v.* antibiotic regimens against the airway pathogen *P. aeruginosa*, also cause vestibular toxicity and ototoxicity [104].

As noted at the beginning of this section, there are a startling number of adverse outcomes associated with exacerbations and their treatment. It is for these reasons that the prevention of pulmonary exacerbations has become a common treatment goal for therapies used routinely to maintain lung health [11, 105].

Conclusion

Pulmonary exacerbation is a frequent and common event in CF lung disease, generally defined as worsening of the daily respiratory and systemic symptoms and an acute drop in pulmonary function. Although there is general agreement on this vague description, there remains no validated prospective definition, and several reasons for this have been outlined here. Despite the lack of a standard definition, pulmonary exacerbations are recognised as an important aspect of CF lung disease.

From a pragmatic perspective, the current best exacerbation definition appears by default to be the physician's decision to treat, as all knowledge of exacerbation-associated risks and treatment outcomes have been derived using some form of this definition and it is simple to collect by asking the question "Why did you treat?" The unavoidable problem with this definition is one of variability among clinicians; an exacerbation treated in one clinic might not be an exacerbation in another, a situation that makes both clinical scientists and regulators understandably uncomfortable. Some discomfort with "objective" exacerbation definitions may simply relate to CF clinician training, which holds that an identified exacerbation should be treated (provided the patient is willing). By extension, a presentation that does not warrant direct intervention is somehow less than an exacerbation. Exacerbation definitions that identify constellations of signs and symptoms that they do not currently treat or, alternatively, that fail to identify patients that they treat today are naturally viewed with suspicion. It may be that the very word "exacerbation" itself, with its firm link to intervention, is part of the problem. An alternative term, such as "transient deterioration", that can identify respiratory events of different grades ranging from mild to severe and that is not so intimately tied to treatment may be necessary to break this impasse.

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Disclosures: None declared.

Chapter 4

Non-cystic fibrosis bronchiectasis: definition, severity and impact of pulmonary exacerbations

Simon Finch, Alison J. Dicker and James D. Chalmers

Exacerbations of bronchiectasis are common, with European data suggesting that the average patient experiences two exacerbations per year. Exacerbations have been associated with worse QoL, lung function decline and increased mortality. Exacerbations are highly heterogeneous, presenting most frequently with increasing cough and sputum production, but also commonly with breathlessness, wheeze, malaise and systemic features. There is a lack of research into the causes of bronchiectasis exacerbations, but antibiotic therapy is currently recommended for all exacerbations because of the high frequency of bacterial infection in the disease. Exacerbations are the primary end-point for the majority of late-phase bronchiectasis clinical trials, although these have been limited by the lack of a standardised definition. The EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) network, in collaboration with colleagues from the USA, Australasia and South Africa, has recently generated a consensus definition of exacerbations, which should help to standardise outcomes. Exacerbations are key events in the natural history of bronchiectasis. There is an urgent need for further research into the causes, optimal management and outcomes of bronchiectasis exacerbations.

Cite as: Finch S, Dicker AJ, Chalmers JD. Non-cystic fibrosis bronchiectasis: definition, severity and impact of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 38–57 [https://doi.org/10.1183/2312508X.10015816].

Bronchiectasis is a chronic respiratory condition characterised by daily productive cough and frequent exacerbations, with little research and no licensed treatments. In recent years, however, there has been a surge in interest in this fascinating and heterogeneous condition.

Exacerbations are major events in the course of the disease. They are characterised by a deterioration in the patient's chronic symptoms, along with new and/or distressing features. Symptoms may come on over hours, days or weeks, and usually prompt a change in treatment. They are associated with poorer prognosis in a number of studies. Our group

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demonstrated that an exacerbation frequency of three or more in the previous year and previous hospitalisations for severe exacerbations were independent predictors of mortality and future hospitalisation [1]. Depending on the population studied, patients have between one and six exacerbations per year, and these are associated with periods of high symptom burden, time off work/school, hospital admissions, deterioration in QoL, increased morbidity and risk of mortality. Reducing exacerbations is a primary focus of clinical care and clinical trials into bronchiectasis. It is perhaps an expected finding in a neglected and poorly studied condition that a precise, widely accepted definition of an exacerbation is not available [2]. Many authors and guidelines have used a variety of definitions in different situations.

In this chapter, we discuss the burden of bronchiectasis and bronchiectasis exacerbations, the clinical features and causes, and finally the critical issue of how exacerbations are defined in clinical trials.

Burden of disease

Bronchiectasis has historically been underdiagnosed, with many patients not under specialist care and potentially mislabelled as having COPD/chronic bronchitis. O'Brien *et al.* [3] found that, in 110 patients diagnosed with COPD in primary care, 32 had bronchiectasis on HRCT, including six patients who had never smoked, suggesting likely misdiagnosis [3]. New epidemiological data suggest that there are many more patients with bronchiectasis than was previously appreciated. Quint *et al.* [4] demonstrated that the prevalence in the UK increased between 2004 and 2013 (from 301.2 per 100 000 population to 485.5 per 100 000 in men, and from 350.5 per 100 000 to 566.1 per 100 000 in women) (figure 1) and that mortality was substantially higher than previously reported (comparative mortality rate of 2.14 for men and 2.26 for women).

Ringshausen *et al.* [5] found a much lower prevalence of 67 cases per 100 000 population in Germany, although the authors acknowledged that, due to the study design, this was likely to be an underestimate. Seitz *et al.* [6] demonstrated an annual increase in the prevalence of bronchiectasis in the USA of 8.74% between 2000 and 2007; in a previous study, they also showed an increase in hospital admissions between 1993 and 2006 of 2.4% per year for men and 3.0% per year for women, with a hospital mortality rate of 4.6% [7]. In 2012, Monteagudo *et al.* [8] found a prevalence in Catalonia of 362 per 100 000, of which 56% had had at least one exacerbation and 12.5% had been admitted to hospital. Niewiadomska *et al.* [9] found an increase in hospital admissions from 95 in 2000 to 374 in 2011 in one region of Poland, while Bibby *et al.* [10], in 2015, showed that, in New Zealand, there were 5494 hospital admissions over 5 years with a 30-day readmission rate of 12.4%, the prevalence varying significantly with ethnicity and socioeconomic deprivation.

Epidemiological data on bronchiectasis in Europe is patchy, and several European countries (Germany, France, Hungary, Ireland, Macedonia, The Netherlands, Romania, Sweden and Turkey) report hospital admission rates for bronchiectasis combined with COPD [11].

Data on the frequency of exacerbations is sparse and is affected by the variable definitions of what an exacerbation is, as described in a later section. Chalmers *et al.* [1] found a mean exacerbation frequency of 1.8 per year across international cohorts. Mortality following admission with an exacerbation can be high, with one study finding a 21% mortality rate at 1 year following admission to hospital with an exacerbation [12].

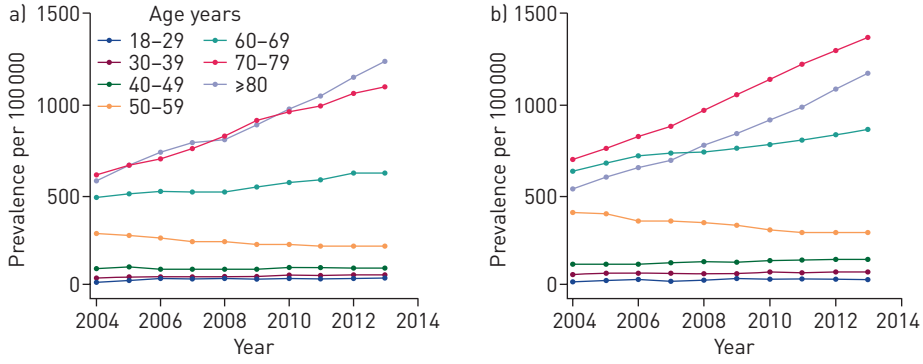

Figure 1. Prevalence of bronchiectasis in the UK between 2004 and 2013 for a) men and b) women. Reproduced and modified from [4] with permission.

Clinical presentation of exacerbations

There are limited published data on the clinical presentation of bronchiectasis. Patients with bronchiectasis are all different and may describe their exacerbations differently. Aliberti *et al.* [13] identified four different phenotypes of bronchiectasis with variable frequency of exacerbation and other symptoms among the groups. The symptoms of one patient will differ significantly from those of their peers; thus, for some with mild disease, sputum production is a minor daily annoyance so a change in volume is a significant event, while for those with severe disease, a large sputum volume might be unremarkable. For patients, an exacerbation is often a uniquely personal feature. Patients with bronchiectasis have chronic daily symptoms of cough, sputum and dyspnoea, so it is important to recognise that a change in these symptoms is significant. It is therefore vital to undertake a thorough assessment of these patients when clinically stable to be able to compare and recognise a change.

Common symptoms reported at exacerbation include increased cough, increased sputum production and a change in sputum characteristics, such as colour, viscosity, ease of expectoration, taste and other features. Patients may become more breathless, or may report wheeze. Chest pain is common in bronchiectasis, particularly with exacerbations [14]. Systemic features such as tiredness/malaise are common. Patients may have upper respiratory tract symptoms, or may have fever.

Unlike in COPD where symptom diaries have been used extensively to model the onset of symptoms and the patterns of exacerbation onset, little is known about how rapidly symptoms of bronchiectasis exacerbations develop. There is a normal day-to-day variation in symptoms of all chronic respiratory diseases. Exacerbation occurs when symptoms exceed the normal day-to-day variation and exceed a threshold of symptom severity that the patient regards as indicative of an exacerbation (the exacerbation threshold).

The most detailed study of exacerbation onset and symptomatology to date was reported by Brill *et al.* [15], who studied 32 patients who completed symptom diaries for a median of nearly 18 months. Their results are shown in figure 2a and b, showing how symptoms and peak expiratory flow changed at exacerbation. Patients developed new symptoms up to

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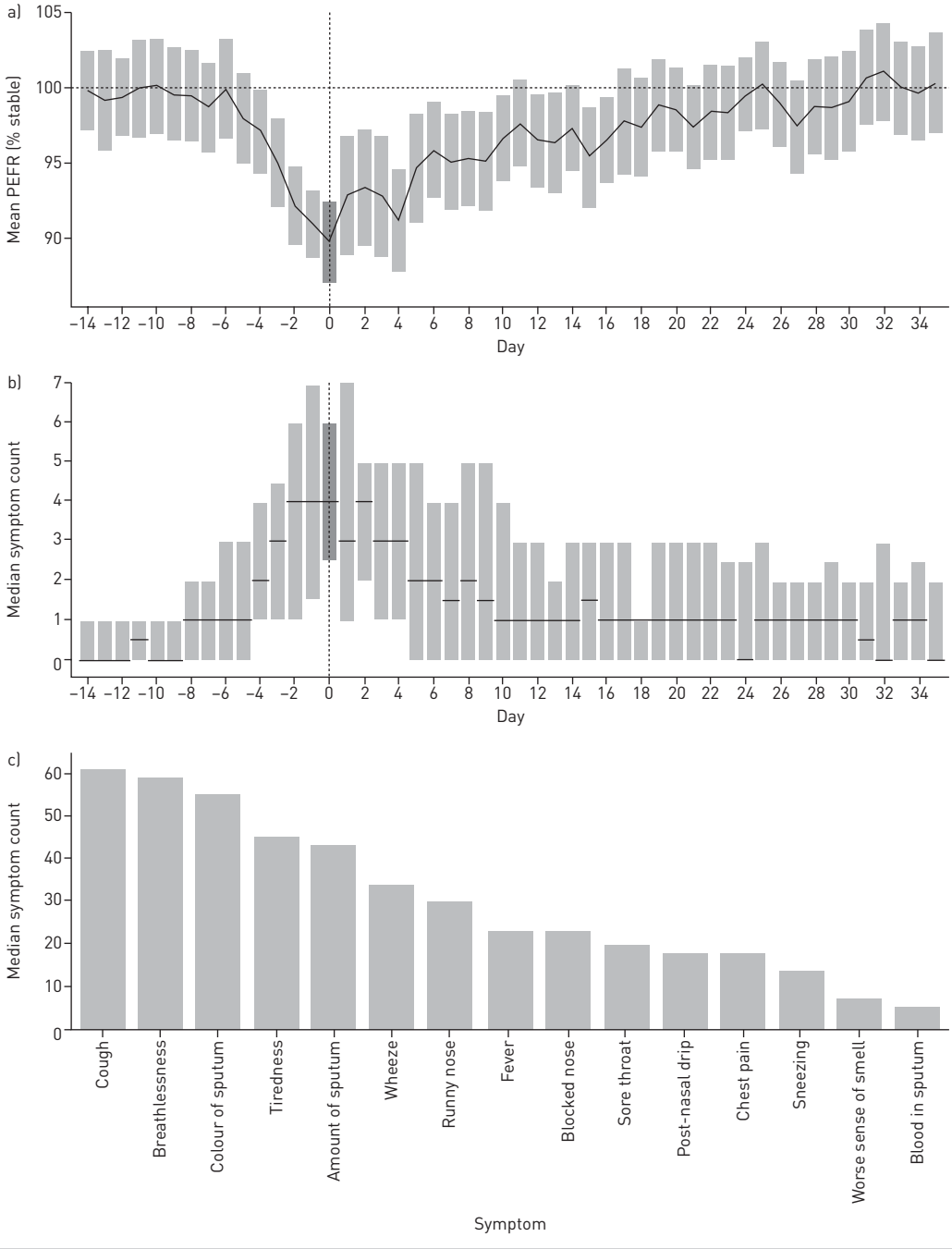

Figure 2. Daily measurements of a) peak expiratory flow rate (PEFR) and b) diary card symptom counts preceding and after the onset of exacerbation. a) The solid line represents the mean PEFR and the bars are the 95% CIs; b) the black lines show the median and the bars are the interquartile ranges. c) Percentage of patients reporting each individual symptom. PEFR: peak expiratory flow rate. Reproduced and modified from [15] with permission.

10 days before reporting exacerbations, and presented at the point that symptoms and lung function changes peaked. Exacerbations were heterogeneous, with multiple different symptoms reported (figure 2c).

Model of symptom variability

Physicians should be aware of the heterogeneous nature of bronchiectasis and the variation in symptoms. We present a conceptual model of exacerbation based on variation in day-to-day symptoms (figure 3). Figure 3a illustrates a patient with four symptoms of variable severity over time, but who never reaches the threshold for reporting an exacerbation. Figure 3b shows a patient who has four variable symptoms, but with one highly troublesome symptom, which reaches the threshold whereby the individual describes an exacerbation and may seek medical attention. Figure 3c illustrates the more classic exacerbation of a patient with a high symptom burden who has a prolonged deterioration in all four symptoms, which with treatment settle down to the patient's usual state of health.

Causes of exacerbations in bronchiectasis

The cause of exacerbations has previously been viewed as an exclusively bacterial event, and consequently guidelines, such as those from the British Thoracic Society (BTS), recommend that all events are treated with antibiotics. Viruses, however, also play an important role, as do other noninfectious causes, such as air pollution. Common bacteria isolated during exacerbation are *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*; however, the role of these organisms is not necessarily clear, as the same organisms are frequently isolated when patients are stable. It is not known whether bacterial exacerbations arise as a result of increased bacterial load of existing bacteria, the acquisition of new bacteria or changes in bacterial virulence. We are now in the era of the "microbiome" where sequencing of the 16S ribosomal RNA gene has revealed polymicrobial infections during both exacerbation and stability in bronchiectasis. Tunney *et al.* [16] showed little change in the microbiota between stability and exacerbation in bronchiectasis patients. Further large studies of the microbiota have failed to clearly describe changes that would be seen as obviously causal [17, 18].

The role that viruses play in exacerbations of bronchiectasis is not fully understood. Gao *et al.* [19] found viruses in 49% of bronchiectasis exacerbations, and noted a higher level of sputum and serum inflammatory markers in virus-positive exacerbations compared with virus-negative events. In addition, although the bacterial density was not different, virus-positive patients were more likely to receive intravenous antibiotics [19]. It is accepted that viral infections lead to changes at the airway mucosa that increase the likelihood of secondary bacterial infection.

Bronchiectasis patients are complex and have multiple comorbidities. A recent pan-European study showed that patients with bronchiectasis have an average of four other major comorbidities, making the recognition of exacerbations complex [20]. Differentiating symptoms due to bronchiectasis, which require antibiotic therapy, from symptoms due to coexisting heart failure, COPD, asthma or connective tissue disease can sometimes be challenging. The role of air pollution and other environmental factors is not yet clear (figure 4).

The association of bronchiectasis and COPD is well documented and merits particular mention. A meta-analysis by Du *et al.* [21] found that 29.5% of patients with COPD had comorbid bronchiectasis. They calculated a pooled OR of 1.97 (95% CI 1.29–3.00) for COPD exacerbations in those with bronchiectasis. Nevertheless, the complexity of this relationship has recently been discussed [22]. The radiological definition of bronchiectasis

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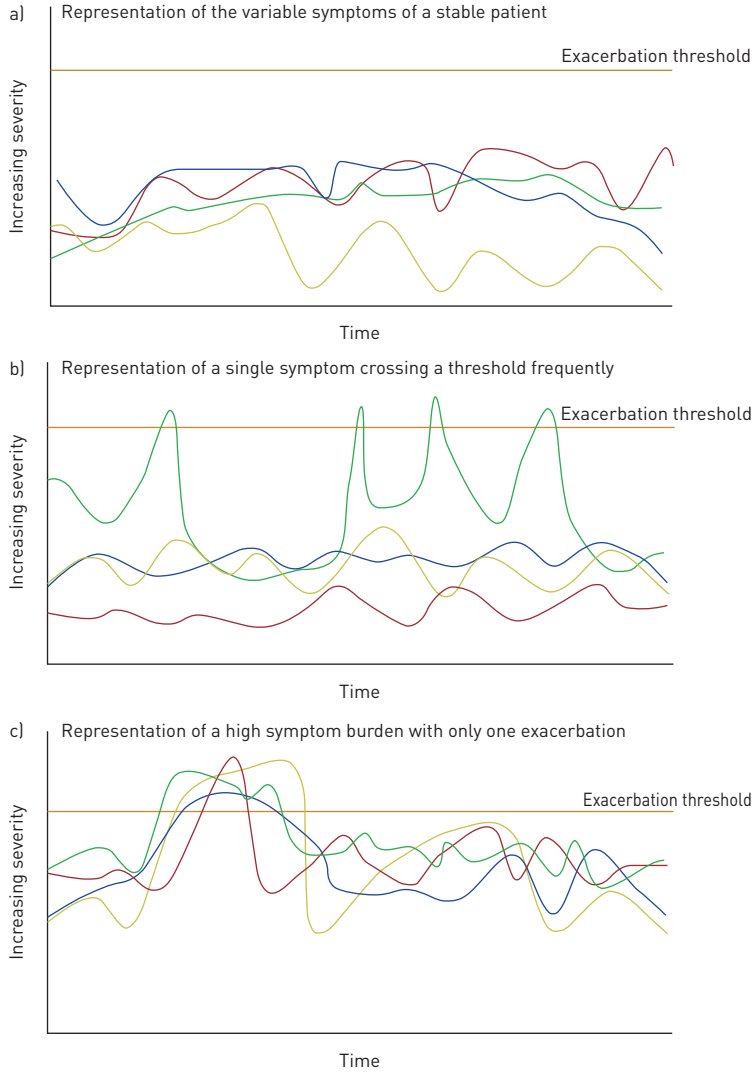

Figure 3. Theoretical model of daily symptom variation and how exacerbations may develop and be reported. Graphic representation of three theoretical patients (a–c) with four arbitrary symptoms showing different patterns.

in COPD is often not clear in studies, and many of the studies to date have systemic biases that ultimately affect the associated meta-analysis. In addition, researchers from the COPDGene group found that apparent radiological bronchiectasis arises from a reduction in vessel size, leading to a falsely elevated bronchial/arterial ratio [22]. There is therefore a lack of clear guidance on how to treat exacerbations in patients with both diseases.

Clinical evaluation of exacerbations of bronchiectasis

Given the heterogeneous nature of bronchiectasis and its aetiology, each patient should be viewed individually. Given the chronic nature of the disease and the frequent exacerbations, many of which may have occurred prior to diagnosis, patients will have their own

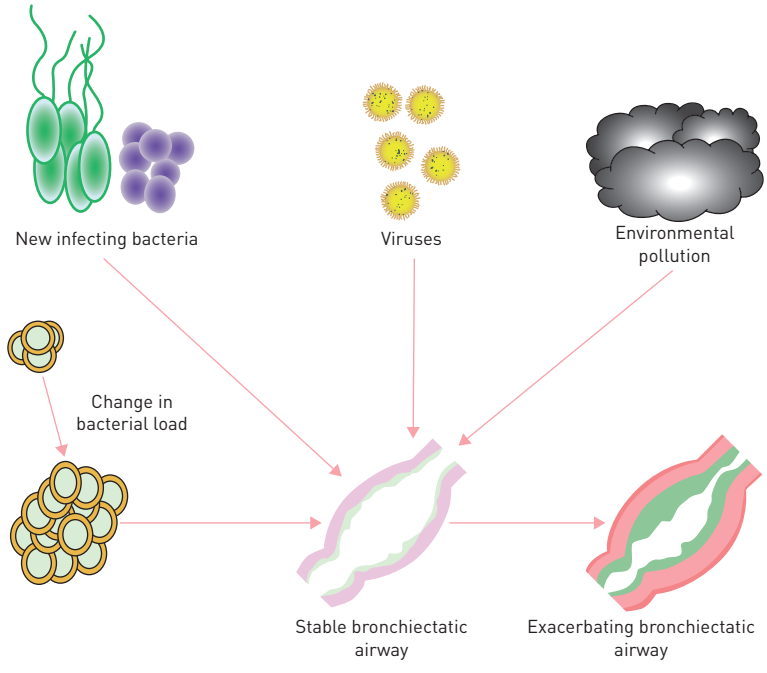

Figure 4. Potential causes of bronchiectasis exacerbations. The exact mechanisms and degree of influence of each factor remain unclear.

perception of what constitutes "my exacerbation". Many clinicians provide patients with bronchiectasis with self-management plans, which foster autonomy through education, support and "rescue medication" [23]. Patients like this autonomy [24], and with any chronic disease, physicians are often keen to facilitate self-management, be this through education, support or by facilitating self-prescription [25]. The BTS includes a recommendation for a self-management plan in their Bronchiectasis Quality Standards [26].

The important issue of antimicrobial stewardship is often at the forefront of the minds of physicians, so there is some anxiety regarding the self-administration of antibiotics and concern about patients misidentifying exacerbations. It is vital that patients feel they have robust education and support to aid in developing confidence with self-management.

The following sections discuss different aspects of the clinical presentation and characterisation of exacerbations.

Physical findings at exacerbation

There are no useful or reliable physical examination features of exacerbations. Patients may have crackles, squeaks or increased work of breathing, but similarly may have these features when stable [27]. These findings are also variable and present in other conditions.

Sputum microbiology

Sputum should be sent for culture at the onset of exacerbation. Initial antibiotic prescribing can be guided by past sputum culture results sent while the patient is stable. The lungs are

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frequently chronically infected in patients with bronchiectasis [28], commonly with *H. influenzae* and *P. aeruginosa*, and this is associated with increased disease severity, reduced QoL and increased frequency of exacerbations [29].

The microbiology may or may not change during any infective exacerbation, such as a change in infecting organism or in the bacterial load of the chronically infected patient. It has been shown that clearance of an infection or a reduction in bacterial load is associated with clinical improvement [30]. However, the turnaround time of standard culture and the limited access to rapid molecular tests make this unlikely to be a feature used for the clinical assessment of an exacerbation at this stage. A negative sputum culture does not exclude exacerbation or the need for antibiotic therapy because of the poor sensitivity of culture.

Sputum characteristics

Sputum colour is a useful feature of the assessment of bronchiectasis and exacerbations, as it is indicative of bacterial infection and neutrophilic inflammation, with a resulting requirement for antibiotic therapy if other clinical symptoms are present.

Murray *et al.* [31] developed a simple sputum colour chart that was shown to be easy to use for both patients and doctors, with a strong degree of agreement between them. Goemmine *et al.* [32] demonstrated a correlation between the sputum colour chart and airway inflammation, disease severity and proteolytic enzyme activity. It is also a useful clinical indicator for assessing resolution of the exacerbation. Hill *et al.* [33] demonstrated that sputum colour will return to its pre-exacerbation state with successful antibiotic treatment.

As well as sputum colour, sputum volume usually increases during an exacerbation. However, sputum volume may be significant in the stable state in bronchiectasis and is hard to measure accurately.

Sputum biomarkers

In many diseases, the "gold standard" in making a diagnosis is a reliable, sensitive biomarker that is cheap and noninvasive (*e.g.* troponin in myocardial infarction). There is much interest in developing such a biomarker in bronchiectasis.

Watt *et al.* [34] demonstrated that, following 14 days of treatment for an infective exacerbation of bronchiectasis, the number of sputum neutrophils was significantly reduced compared with day 0. They also demonstrated that TNF-α, CXCL8 and neutrophil elastase were reduced following antibiotic treatment. Goeminne *et al.* [32] also showed that bronchiectasis patients had significantly higher levels of sputum neutrophils, CXCL8, TNF-α, neutrophil elastase and total gelatinolytic activity than controls. Patel *et al.* [35] showed that patients with bronchiectasis have higher levels of sputum IL-6 and IL-8 than those with COPD or normal controls. However, Ayhan *et al.* [36] found that, while CXCL8 levels in sputum were elevated in bronchiectasis, IL-6 levels were not.

Chalmers *et al.* [37] recently showed that elevated sputum neutrophil elastase was associated with more frequent exacerbations and a shorter time to next exacerbation. The related serum marker desmosine was also measured and shown to correlate with sputum neutrophil elastase and also with the rate of severe exacerbations (but not with moderate exacerbations).

These are not routinely available tests, and so their value in routine clinical practice is not yet known. There is ongoing research looking at these sputum biomarkers, with the addition of neutrophil extracellular traps as a marker of interest as they have been shown to be raised in asthma and COPD [38, 39].

Exhaled gases

There has been some interest in measuring exhaled gases as a noninvasive measure of airway inflammation.

Loukides *et al.* [40] showed that patients with stable bronchiectasis had exhaled hydrogen peroxide (H_2O_2) levels that were higher than normal controls; they also demonstrated a negative correlation between H_2O_2 levels and FEV1 [41]. The levels were not affected by the use of inhaled corticosteroids. Exhaled H_2O_2 is also raised, however, in various other chronic respiratory conditions, and can be affected by ambient air concentrations [42]. There has also been some interest in the past in exhaled carbon monoxide and nitric oxide in bronchiectasis [43, 44], but this research has not progressed.

Radiology

HRCT has surpassed plain radiography in the diagnosis of bronchiectasis [45, 46]. Signs seen on chest radiographs, such as tram tracks or ring shadows, reflect dilated and thickened bronchial walls. Such changes are usually not detectable on chest radiography in mild disease. There is an important role for chest radiography in the clinical assessment of a bronchiectasis exacerbation for detecting mucus plugging or collapse, and for the exclusion of other pathologies, such as pneumonia/empyema, or the detection of complications, such as pleural effusions. However, a chest radiograph during an exacerbation could be unchanged from stability, or may show nonspecific signs. It is not necessary to perform radiography for the majority of bronchiectasis exacerbations treated in an outpatient setting.

Spirometry

Spirometry has an important role in the long-term management and assessment of patients, particularly in assessing severity and identifying deteriorating patients [1]. Nevertheless, it is not a reliable feature of exacerbation. Murray *et al.* [30] showed no effect of exacerbations on spirometry and no improvement in spirometry after 14 days of antibiotic treatment, in contrast to CF where lung function changes are frequently seen with exacerbation. Brill *et al.* [15], however, showed clear changes in peak expiratory flow in some patients at exacerbation in their small study. There is not yet a clear role for spirometry in the assessment of exacerbations.

QoL questionnaires

QoL questionnaires are a useful tool both for research and in routine clinical practice. Questionnaires previously created for other purposes have been adapted and validated for use in bronchiectasis. The St George's Respiratory Questionnaire has been validated in bronchiectasis and used extensively [47]. The Leicester Cough Questionnaire has been validated in bronchiectasis in several different languages [48–50]. The Quality of

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Life-Bronchiectasis questionnaire was published in 2014 as the first bronchiectasis-specific QoL assessment tool, and has since been validated [51, 52].

While QoL questionnaires are highly useful in the routine assessment of chronic disease, their role in the assessment of an exacerbation is limited, they are often time-consuming to administer and they are not designed for use during an acute illness where other features are more likely to be of benefit. Equivalents of EXACT-PRO (Exacerbations of chronic pulmonary disease tool 14-item patient-reported outcome) symptom diaries used in COPD to define exacerbations do not yet exist in bronchiectasis.

Risk of future exacerbations

Some patients with bronchiectasis experience frequent exacerbations, while others rarely exacerbate. Identifying patients at high risk of exacerbations is crucial for clinical management in order to properly target preventative therapies. A number of risk factors have been identified for exacerbation and are summarised here. The Bronchiectasis Severity Index (BSI) [1] is a highly validated score that predicts the risk of poor outcomes; it stratifies patients into mild, moderate and severe. The risks of hospitalisation for a bronchiectasis exacerbation at 1 and 4 years are 0–3.4% and 0–9.2% for mild, 1–7.2% and 9.9–19.4% for moderate, and 16.7–52.6% and 41.2–80.4% for severe patients, respectively. There are several features included in the BSI that individually increase the risk of further exacerbations: FEV_1 <30%, a Medical Research Council (MRC) dyspnoea score of 4/5, chronic infection with *Pseudomonas* or any other bacterium, and the radiological severity of bronchiectasis have been individually linked to future events. Nevertheless, the strongest predictor of future events is a past history of events. The BSI has an accuracy of 76–88% for predicting future severe exacerbations.

Bronchiectasis is predominantly a disease of older people [4]. Older patients tend to have more comorbidities and poorer QoL, and die more frequently. A lower body mass index, previous hospitalisations and decreasing FEV_1 are associated with increased risk of death [53].

Patterns of spirometry vary in bronchiectasis, and one small study found that patients with normal spirometry are less likely to be admitted to hospital than those with restrictive or obstructive spirometry (17% over 2 years compared with 27.3% (restrictive) and 32.6% (obstructive)) [54].

Chronic infection with *P. aeruginosa* or any other organism increases the risk of exacerbation. Given the significantly poorer outcomes associated with *P. aeruginosa*, it is assigned a greater weight on the BSI score, and a meta-analysis showed that it was associated with an average of one additional exacerbation per patient per year [29].

Recently, our group demonstrated that a higher neutrophil elastase level in sputum was associated with a higher BSI score, MRC dyspnoea score and radiological extent of bronchiectasis, and with a lower FEV_1 [37]. We also showed that, during follow-up, a higher sputum neutrophil elastase level was associated with a higher frequency of exacerbations and a higher rate of decline of FEV_1 [37].

Additional described predictors of increased exacerbations include higher airway bacterial loads [55, 56]. Other independent predictors of exacerbation were older age, longer

duration of symptoms, lower FEV1, isolation of *P. aeruginosa* and radiological extension [56]. A recent study from China found that patients with coexisting asthma had a higher risk of exacerbations compared with those without asthma [57].

There is initial evidence of genetic susceptibility to increased exacerbations. Mannose-binding lectin is an important component of the innate immune system, and our group showed that deficiency of mannose-binding lectin was associated with an increased risk of recurrent infections [58], while in patients with bronchiectasis it has been shown to be associated with more severe disease, worse QoL, more hospital admissions and exacerbations, and more chronic infection (including *P. aeruginosa*) [59].

Vitamin D deficiency has also been associated with more severe disease, more chronic bacterial infection and more frequent exacerbations [60].

Severity of exacerbations

Many bronchiectasis exacerbations can be simply treated at home with oral antibiotics. BTS guidelines advise inpatient care if the patient develops respiratory failure, hypercapnia, tachypnoea (>25 breaths·min^{-1}), haemodynamic instability or cognitive deterioration [46]. These features clearly describe a very unwell patient whose presentation to their primary care physician in this state is likely to prompt admission to hospital. They also advise admission due to inability to cope at home. Given that a large number of bronchiectasis patients are elderly [4] and comorbid [53], this simple issue is likely to be a frequent consideration. Elderly patients may have difficulty in taking oral treatment, necessitating admission, and frailty in itself may make admission necessary for an exacerbation that causes only minor systemic disturbance.

Other features that may prompt an inpatient stay have been suggested, including fever (>38°C) and haemoptysis. Haemoptysis is often a feature of bronchiectasis [61] and may be a fairly minor event. Neovascularisation is a dangerous feature of long-term severe bronchiectasis, and is seen in bronchiectasis where major bleeding requiring surgical or radiological intervention can occur.

i.v. antibiotics are traditionally administered as an inpatient, although in many healthcare systems there is some availability of home *i.v.* antibiotic services [62]. Home *i.v.* administration represents a useful advance in reducing costs to the healthcare provider, as well as inconvenience to patients. The BTS recommends the provision of home *i.v.* antibiotics when this is appropriate [26].

The patterns of microbial infection and resistance mean that antibiotic choices can be limited, and *i.v.* antibiotics may represent the only choice, for example for multidrug-resistant *P. aeruginosa* or other difficult Gram-negative organisms, such *Stenotrophomonas maltophilia*. The decision to admit may be influenced by apparent failure of outpatient orally administered treatment. As stated previously, obtaining a sputum sample for culture in all cases of exacerbation is vital. Empirical treatment guided by previous sputum culture results should be started immediately once it is deemed necessary, and a sputum sample obtained. In the case of treatment failure, accurate and considered assessment of the microbiology will play a vital role. Sputum culture results may take several days to become available, so acute prescriptions cannot be delayed.

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Admissions to critical care for bronchiectasis exacerbations are very rare, making up only 0.1% of UK ICU admissions over 4 years [63]. The same review found that admission rates to the ICU increased at a rate of 8% per year, and that mortality was significantly higher in patients with bronchiectasis compared with similar patients with COPD (23.1% *versus* 31.1% for ICU mortality and 36.4% *versus* 46.6% for in-hospital mortality, respectively) [63]. It is important to include comprehensive care for severe exacerbations in hospital. Attention should be paid to airway clearance, hydration, nutrition, oxygen and the treatment of bronchospasm in addition to antibiotics.

Impact of exacerbations

Each exacerbation of bronchiectasis represents a significant event in a patient's life. Each will be associated with an increase in the already heavy symptom burden that they suffer, a change in treatment and a reduction in QoL. Brill *et al.* [15] found that median recovery time was 9 days after starting treatment; however, 16% of patients were still symptomatic after 35 days.

Patients with frequent exacerbations have an increased long-term mortality, an increase in the risk of hospital admissions and poorer QoL, and there is some evidence that exacerbations can contribute to lung function decline and therefore one aspect of disease progression. Exacerbations also have an important impact on the healthcare system in terms of healthcare costs.

Bronchiectasis is associated with an increase in mortality compared with the general population. Loebinger *et al.* [64] collected data on mortality over 14 years of follow-up; 30% of the cohort died over this period, representing a >2-fold increase over the expected mortality for the healthy population, with 70% of deaths due to respiratory causes. There is also a high rate of death from cardiovascular causes. Iwagami *et al.* [65] found that there was an increasing incidence of acute kidney injury in patients admitted with an exacerbation of bronchiectasis in the UK, rising from just under 2% in 2004 to nearly 5% in 2013. Our group found an annual frequency of between 1.8 and three exacerbations per year with a hospitalisation rate of 26.6–31.4% [1]. A single night in a National Health Service hospital in the UK is estimated to cost GBP400 [66], while the costs in Europe range from USD349 to USD2394 [67]. De la Rosa *et al.* [68] found that the annual cost of treating a patient with bronchiectasis was EUR4671.90, and that costs increased with the severity of the disease. They also found that, in patients with moderate or severe disease, it was exacerbations that had the most impact on costs. Bibby *et al.* [10] estimated that the annual costs for treating bronchiectasis in New Zealand was NZD5.34 million (for hospital admission alone).

This important impact on patients and the healthcare system is the reason why exacerbations are the most frequent end-point for definitive trials of new therapies in bronchiectasis.

Exacerbations in clinical trials

Exacerbation frequency, time to next exacerbation and severity of exacerbation are important end-points that have been used in research studies as primary and secondary end-points. While sputum microbiology and biomarkers have the potential to provide vital and fascinating insights into the pathophysiology of bronchiectasis and may be used as end-points in phase II studies, QoL and exacerbations are the most suitable end-points for definitive studies.

Regulators and investigators require confidence that such end-points are robustly defined in order to have confidence in treatment effects. Until recently, there has been no widely accepted definition of what constitutes a bronchiectasis exacerbation. Many different authors have used various definitions to suit their purposes. Some definitions have been used in only a single study and others much more widely. It is acknowledged that the lack of a clear and widely used definition can affect the quality of research [69]. We have found >15 different definitions used in bronchiectasis clinical trials to date, which are summarised in table 1, along with examples of studies that have used this definition. This table is not exhaustive, but it serves as an example of the variety of definitions used. Each of these definitions has pros and cons. When used in retrospective studies, the use of a pragmatic definition is often a necessity and acknowledges the importance of clinical judgement. Some definitions are significantly more complex than others, which has a disadvantage in both research and routine clinical practice. In general, regulators will require studies that are aiming for the registration of drugs to use a robust objective definition of exacerbation.

The variety of different definitions reflects the need for consensus, and many authors comment on this need, particularly for research, as other authors have sought consensus in defining exacerbation of COPD [94].

Given the complex nature of bronchiectasis and the heterogeneous nature of exacerbations, and in the spirit of the excellent collaborative work taking place in bronchiectasis research internationally, a new consensus definition of exacerbation has recently been proposed [95]. A panel of experts, organised by the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), from across Europe, the USA, Australia, South Africa and New Zealand convened during the 1st World Bronchiectasis Conference in Hannover on July 7, 2016. They considered the variety of definitions used previously. Their aim was to produce a definition robust enough for use in clinical trials. The panel unanimously agreed the definition as: "a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 hours: 1) cough, 2) sputum volume and/or consistency, 3) sputum purulence, 4) breathlessness and/or exercise tolerance, 5) fatigue and/or malaise, 6) haemoptysis, AND a clinician determines that a change in bronchiectasis treatment is required" (figure 5).

It is important to emphasise that this definition is proposed for use in clinical trials only. There is some utility in using this definition in clinical practice, but there is likely to be some appropriate degree of flexibility required, particularly with regard to autonomy and self-management, and in some cases patients will need to be treated before 48 h have elapsed. This definition uses three symptoms to help avoid overtreating a single symptom, and includes a timescale that should avoid treating the brief illnesses that can mimic an exacerbation [95].

As with all concepts derived from expert opinion, this definition requires prospective validation, but wide use of a single definition will at least allow comparison of results among different studies and greater confidence in treatment effects.

Conclusion

Exacerbations are a defining feature of the clinical syndrome of bronchiectasis. Both the disease and the exacerbations are, however, highly heterogeneous. A clear definition of an

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Table 1. Definitions of bronchiectasis used in clinical trials

First author [ref.]	Definition	Comment
Pasteur [46]	A change in one or more of the common symptoms of bronchiectasis (increasing sputum volume or purulence, worsening dyspnoea, increased cough, declining lung function, increased fatigue/malaise) or the appearance of new symptoms (fever, pleurisy, haemoptysis, requirement for antibiotic treatment).	Appropriate for clinical practice, but unlikely to be accepted by regulators as it is very broad.
Vendrell [70]	The acute development and persistence of changes in sputum characteristics (increased volume, thicker consistency, greater purulence, or haemoptysis), and/or increased breathlessness unrelated to other causes.	Takes the view that an exacerbation cannot occur without a change in sputum characteristics.
Haworth [71]	Increase in cough frequency, sputum volume, sputum viscosity. May also complain of chest tightness, wheeze and breathlessness. Other common features include streaky haemoptysis, chest discomfort and temperature.	
Bilton [72], Chalmers [55], Kellett [73], Wilson [74]	Various pragmatic descriptions, *e.g.* hospital admission, a change in treatment or an antibiotic prescription.	
Courtney [75]	A clinical decision to treat with intravenous antibiotics was made because of increased cough, sputum production or breathlessness.	
Altenberg [76]	An increase in respiratory symptoms requiring antibiotic treatment.	The BAT (Bronchiectasis and long-term azithromycin treatment) trial [76].
Modified Fuchs criteria	Deterioration in at least four of the following features: sputum production (consistency, colour, volume or haemoptysis), dyspnoea, cough, fever, wheeze, exercise tolerance, fall of $\geqslant$10% in FEV_1 or FVC, new changes on chest radiograph, or changes in chest signs on auscultation.	Used in many different studies; originally designed for CF [77–81]
Wong [82]	Increase in or new onset of more than one pulmonary symptom (sputum volume, sputum purulence, or dyspnoea) requiring treatment with antibiotics.	Used in EMBRACE (Effectiveness of macrolides in patients with bronchiectasis using azithromycin to control exacerbations) trial [82].

Continued

Table 1. Continued

First author [ref.]	Definition	Comment
Anthonisen [83]	Increased dyspnoea, sputum production and sputum purulence.	Originally used for COPD studies and widely adapted to bronchiectasis [31, 84, 85].
Hernando [86]	Worsening of three of the following symptoms: cough, sputum, dyspnoea or fever.	
Lee [87]	Four or more signs and symptoms (including change in sputum amount, thickness or colour, haemoptysis, increased cough, tiredness, shortness of breath or fever >38°C) for ⩾2 consecutive days with and without prescription of new antibiotics.	
Bilton [88]	Presence of at least two of the following symptoms: increased cough, increased volume of sputum produced, increased sputum purulence (3 on sputum colour card), increased dyspnoea or increased wheezing. Plus at least one of the following symptoms: fever (temperature >38°C), malaise, increased white blood cell count, increased serum CRP level or erythrocyte sedimentation rate when compared with screening values Plus laboratory evidence of purulent sputum defined by >25 white blood cells per low-power field and <10 squamous oropharyngeal epithelial cells at ×100 magnification.	
Barker [89]	At least three major (or two major and at least two minor) criteria. Major criteria were increased sputum production, change in sputum colour, dyspnoea and cough. Minor criteria were fever (>38°C) at clinic visit, increased malaise or fatigue, FEV_1 or FVC decreased by >10% from baseline, and new or increased haemoptysis.	
Nicolson [90]	Three of the following symptoms for 2 days: change in sputum volume or colour, new or increased haemoptysis, increased cough, dyspnoea, lethargy, fever or increased sinus discharge.	

Continued

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Table 1. Continued

First author [ref.]	Definition	Comment
Serisier [91]	Requires antibiotic administration for a sustained (>24 h) increase in sputum volume or purulence accompanied by new deteriorations in at least two additional symptoms: sputum volume, sputum purulence, cough, dyspnoea, chest pain, or haemoptysis.	The BLESS (Bronchiectasis And Low-Dose Erythromycin Study) trial.
Haworth [92]	Three or more of the following signs or symptoms for at least 24 h: increased cough, increased sputum volume, increased sputum purulence, haemoptysis, increased dyspnoea, increased wheezing, fever (>38°C) or malaise, and the treating physician agreed that antibiotic therapy was required.	
Tsang [93]	Subjective and persistent (>24 h) deterioration in at least three respiratory symptoms including: cough, dyspnoea, haemoptysis, increased sputum purulence or volume, and chest pain; with or without fever (>37.5°C), radiographic deterioration, systemic disturbances, or deterioration in physical signs in the chest including crackles and dullness on auscultation and percussion, respectively.	

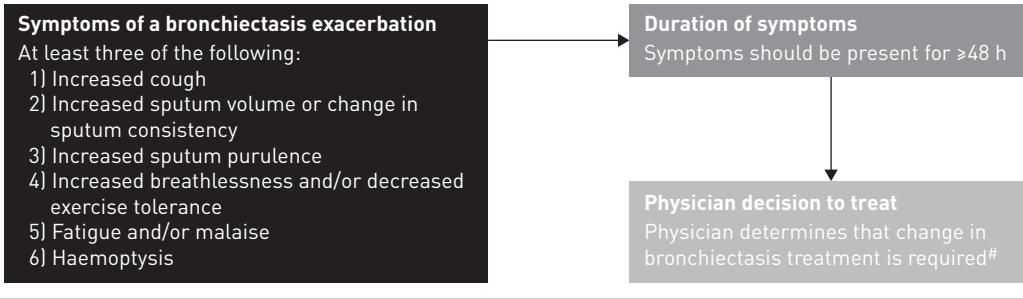
Symptoms of a bronchiectasis exacerbation
At least three of the following:
1) Increased cough
2) Increased sputum volume or change in sputum consistency
3) Increased sputum purulence
4) Increased breathlessness and/or decreased exercise tolerance
5) Fatigue and/or malaise
6) Haemoptysis
Duration of symptoms
Symptoms should be present for ⩾48 h
Physician decision to treat
Physician determines that change in bronchiectasis treatment is required#

Figure 5. Consensus definition of bronchiectasis exacerbations for use in clinical trials. #: physicians should exclude other causes of deterioration in symptoms.

exacerbation is needed to aid both clinical practice and future research. There have previously been many different definitions used, but a strict definition for use in clinical trials has recently been agreed upon by an international panel of experts.

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Disclosures: S. Finch has received personal fees from Napp, outside the submitted work. J.D. Chalmers has received financial support, outside the submitted work, from Bayer HealthCare and Aradigm Corporation for the European Bronchiectasis Registry. J.D. Chalmers has received grants, outside the submitted work, from Novartis Pharmaceuticals and Basilea as a member of the IABC consortium, a European Union Innovative Medicines Initiative Consortium. J.D. Chalmers has also received the following, outside the submitted work: grants and personal fees from AstraZeneca, Boehringer Ingelheim and Pfizer, a grant from GlaxoSmithKline and personal fees from Napp and Chiesi.

Chapter 5

IPF: definition, severity and impact of pulmonary exacerbations

Kiminobu Tanizawa[1], Harold R. Collard[2] and Christopher J. Ryerson[3]

A recent international working group has suggested redefining AE of IPF (AE-IPF) as an acute, clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormality. These revised diagnostic criteria consist of: 1) previous or concurrent diagnosis of IPF, 2) acute worsening or development of dyspnoea typically of <1 month duration, 3) CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with a usual interstitial pneumonia pattern and 4) deterioration not fully explained by cardiac failure or fluid overload. This represents a major change from the previous definition and diagnostic criteria, most significantly in no longer requiring AEs to be idiopathic. Historically, the annual incidence of AE-IPF ranges between 1% and 20%, and AEs have an in-hospital mortality of 27–65%. Multicentre registries and networks are necessary to revisit the epidemiology of AE using the revised definition, further define the risk factors for AE, and develop both preventative and therapeutic management approaches.

Cite as: Tanizawa K, Collard HR, Ryerson CJ. IPF: definition, severity and impact of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 58–65 [https://doi.org/10.1183/2312508X.10015916].

The definition of IPF is a progressive interstitial lung disease (ILD) of unknown cause that is characterised by a radiological and/or pathological pattern of usual interstitial pneumonia (UIP) [1]. Nintedanib and pirfenidone are oral therapies that slow the rate of lung function decline in patients with mild to moderate IPF [2–4]; however, IPF remains a fatal disease with a reported median survival of approximately 3 years from the time of diagnosis [5].

The natural history of IPF remains poorly characterised. Historically considered a disease of gradual decline in physiology over years, IPF is now known to be less predictable, and many patients may experience acute respiratory worsening that develops over a span of days to weeks. This worsening is referred to as an AE of IPF (AE-IPF) if specific diagnostic

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criteria are met. AE-IPF is an important clinical event for patients with IPF, with significant associated morbidity and mortality. This chapter will provide clinicians and researchers with an update on the definition, severity and impact of AE-IPF.

Definition

The definition and diagnostic criteria of AE-IPF have evolved over the last two decades (table 1) [6–8]. AE-IPF has typically been defined as an acute worsening or recent onset of dyspnoea with new bilateral ground-glass opacity and/or consolidation on HRCT in a patient with previously or concurrently diagnosed IPF. Differences among previous criteria have included a timeline of worsening dyspnoea and the need to objectively confirm worsening oxygenation.

The Japanese Ministry of Health, Labour and Welfare Diffuse Pulmonary Disease Research Group proposed criteria for AE-IPF that were published in 2004 [6]. In addition to typical symptoms and radiological features, these criteria included a decrease in P_{aO_2} of ⩾10 Torr from baseline, thus requiring an arterial blood gas obtained during a previous stable phase. These criteria also required AE-IPF cases to be idiopathic, excluding patients with identifiable triggers, such as infection and pulmonary embolism.

The National Institutes of Health-sponsored IPF Clinical Research Network (IPFnet) in the USA proposed a definition and diagnostic criteria for AE-IPF that were published in 2007 [7]. This group defined AE-IPF as an acute, clinically significant deterioration of unidentifiable cause in a patient with underlying IPF. The proposed diagnostic criteria were similar to the 2004 Japanese criteria, although without the need to demonstrate a decrease in P_{aO_2} compared with baseline and with the requirement to exclude more explicitly pulmonary infection by endotracheal aspirate or bronchoalveolar lavage (BAL). These

Table 1. Commonly used definitions and diagnostic criteria for AE of IPF

	Japanese Respiratory Society (2004) [6]	IPFnet (2007) [7]	International working group (2016) [8]
Diagnosis of IPF	Previous	Previous or concurrent	Previous or concurrent
Time window, within	1 month	30 days	Acute (typically 1 month)
New or increasing dyspnoea	✓	✓	✓
CT: new GGOs and/or consolidation on UIP	✓[#]	✓[#]	✓
P_{aO_2} decline ⩾10 Torr	✓		
Exclusion of:			
Infections	✓	✓[¶]	
Isolated congestive heart failure/volume overload	✓	✓	✓
Extraparenchymal causes[+]	✓	✓	✓

IPFnet: National Institutes of Health-sponsored IPF Clinical Research Network; GGOs: ground-glass opacities; UIP: usual interstitial pneumonia. [#]: HRCT is required; [¶]: endotracheal aspirate or bronchoalveolar lavage is required; [+]: *e.g.* pneumothorax, pulmonary embolism.

criteria also defined "suspected AE-IPF" as a deterioration of IPF with an unknown cause that did not meet the criteria for AE-IPF due to missing data (*e.g.* without BAL or endotracheal aspirate).

In 2016, an international multidisciplinary working group proposed an update to the definition and diagnostic criteria for AE-IPF based on data that had accumulated since 2007 [8]. The updated definition of AE-IPF in this document was an acute, clinically significant respiratory deterioration characterised by evidence of new, widespread alveolar abnormality. Similar to the Berlin definition for acute respiratory distress syndrome [9], patients with extraparenchymal causes of respiratory worsening (*e.g.* pneumothorax, pleural effusion, pulmonary embolism) and isolated cardiac failure or fluid overload were excluded, given the distinct pathobiology and favourable prognosis associated with these conditions (figure 1). Compared with previous recommendations, the major change in the 2016 definition of AE-IPF was removal of the requirement for events to be idiopathic, thus allowing inclusion of triggered events, provided other diagnostic criteria were met. This change was based on the clinical, radiological, pathological and prognostic similarities between idiopathic and nonidiopathic events [10, 11]. In addition, the 2007 criteria were often difficult to satisfy, given the frequent inability to perform bronchoscopic or endotracheal evaluation for infection, resulting in a large proportion of "suspected" AE-IPF diagnoses [11, 12]. Although AE-IPF was no longer a necessarily idiopathic event in the 2016 definition, subcategorisation of AE-IPF by "idiopathic" or "triggered" was proposed to reflect the potential management implications of identifying a specific cause of the respiratory worsening and the possibility that idiopathic events still represent a pathobiologically unique subgroup.

The 2016 international working group identified several additional aspects of AE-IPF diagnosis and classification that require further study, and the authors anticipated that future

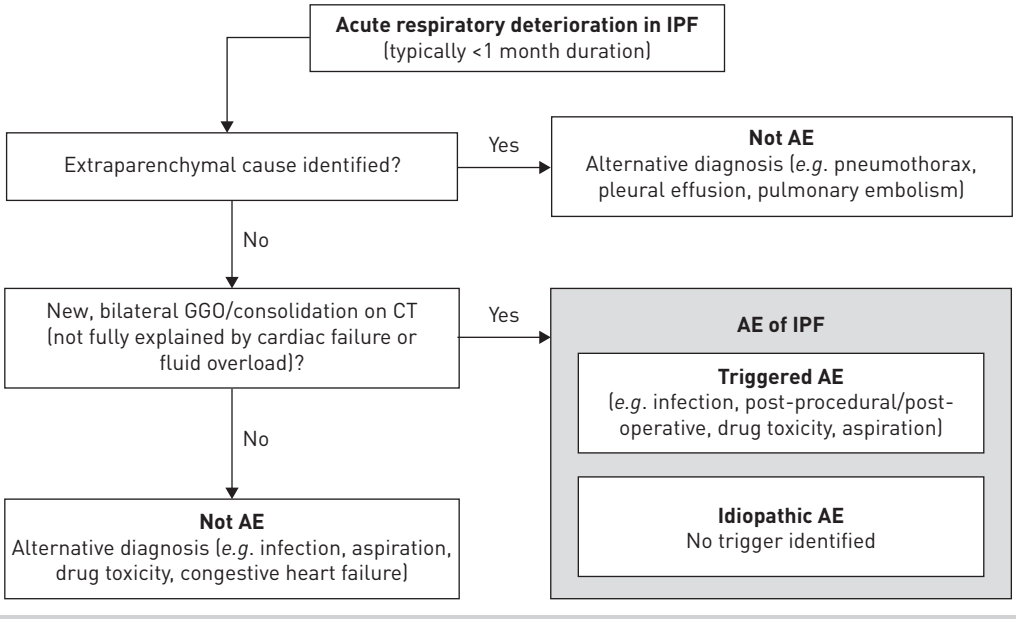
Acute respiratory deterioration in IPF
(typically <1 month duration)
Extraparenchymal cause identified?
Yes
Not AE
Alternative diagnosis (e.g. pneumothorax, pleural effusion, pulmonary embolism)
No
New, bilateral GGO/consolidation on CT (not fully explained by cardiac failure or fluid overload)?
Yes
AE of IPF
Triggered AE
(e.g. infection, post-procedural/post-operative, drug toxicity, aspiration)
Idiopathic AE
No trigger identified
No
Not AE
Alternative diagnosis (e.g. infection, aspiration, drug toxicity, congestive heart failure)

Figure 1. Approach to acute respiratory worsening in patients with IPF. GGO: ground-glass opacity. Reproduced from [8] with permission.

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data would be used to refine the proposed criteria [8]. First, acute respiratory worsening can occur in other chronic fibrotic ILDs, including idiopathic nonspecific interstitial pneumonia, connective tissue disease-associated ILD and chronic hypersensitivity pneumonitis [13–15]; however, the 2016 AE-IPF working group concluded that there was currently insufficient literature to support extension of AE-IPF diagnostic criteria to non-IPF ILDs. Second, the 2016 working group proposed that AE-IPF events should be characterised by worsening that was "typically less than 1 month in duration", allowing for inclusion of events that are believed to be AE-IPF despite falling outside the fixed 30-day interval proposed in the 2007 criteria; however, it is unclear how this more flexible interval will impact the heterogeneity of AE-IPF. Finally, quantitative worsening (*e.g.* a change in oxygenation from baseline) has been used in some previous criteria, but the 2016 working group concluded that such a criterion was not supported by the existing literature and was impractical, given the requirement for available and recent baseline assessments.

Severity

AE-IPF is defined by increased or newly developed dyspnoea that progresses over ~1 month, typically associated with significant hypoxaemia that prompts urgent medical evaluation. In many cases, patients present with respiratory failure requiring admission to hospital and often consideration of mechanical ventilation [16, 17]. Cough, sputum production and fever occur in many patients, often in the absence of a confirmed infection [11, 17]. Patients may also present with features suggesting an underlying trigger, including infection, aspiration [10, 11, 17–20] and new medication use [21–23], and following thoracic surgical procedures [24–26], In addition, AE-IPF may be more common in patients with more advanced disease, during the winter [11, 27, 28], and during times and in regions with worse air quality [29].

The radiological features of AE-IPF include new bilateral ground-glass opacity and/or consolidation superimposed on fibrosis that previously or currently meets radiological and/or histopathological criteria for a UIP pattern (figure 2) [8, 30–34]. The extent of ground-glass opacity and consolidation ranges from 26% to 64% of the total parenchyma [17, 34, 35] and is often >50% [33]. Patients can have a superimposed radiological pattern of diffuse, peripheral or multifocal ground-glass opacity [33, 34, 36], although there is no known biological distinction between these patterns and no clear association with prognosis [34, 35].

Surgical lung biopsies are generally avoided in AE-IPF due to the limited therapeutic utility of characterising the underlying pathological pattern and the high perioperative mortality in this setting [8, 12, 37]. When biopsies are performed, AE-IPF is typically characterised by diffuse alveolar damage superimposed on a UIP pattern [8, 10, 11, 13, 30, 33, 34, 38–40], with some patients having concurrent organising pneumonia that can be the predominant superimposed pattern in a minority of patients [6, 30, 31, 33, 34, 38, 39]. BAL can be used to evaluate for a potential infectious aetiology, but cellular analysis typically shows elevated percentages of neutrophils and lymphocytes that are similar to stable IPF [10, 14, 19, 41].

Impact

The annual incidence of AE in patients with IPF ranges between 1% and 20%, with increased risk seen in patients with more physiologically advanced disease. Importantly,

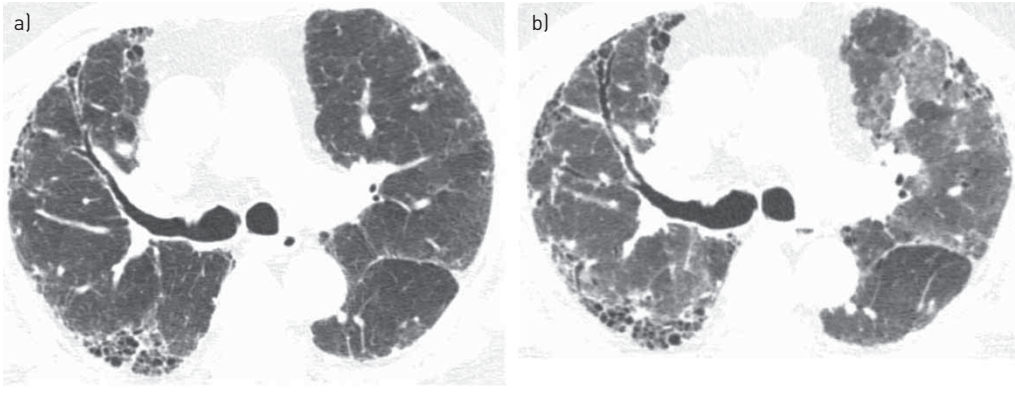

Figure 2. HRCT of AE of IPF. a) CT from a patient before an AE showing a usual interstitial pneumonia (UIP) pattern with subpleural reticulation, traction bronchiectasis and honeycombing. b) CT from the same patient during an AE showing new bilateral ground-glass opacities superimposed on a UIP pattern.

there is significant variability across different populations and study designs [12]. In general, the investigator-reported incidence in cohort studies is slightly higher than that in clinical trials.

A previous meta-analysis of six clinical trials suggested an annual incidence of 4% using the 2007 diagnostic criteria [42], while some cohort studies report an annual incidence of 10–20% [16–18]. A recent *post hoc* analysis of three IPFnet trials found that only 33% of investigator-reported AEs met the 2007 diagnostic criteria following central adjudication, with most cases excluded due to missing data or diagnoses other than AE-IPF [43]. Some of these cases would meet the 2016 AE-IPF criteria that do not require events to be idiopathic, suggesting that the annual incidence may be substantially higher than previously reported.

AEs have a significant impact on the overall prognosis of IPF [10, 44–46], with one Japanese epidemiological study suggesting that AE accounts for up to 40% of all deaths in patients with IPF [47]. In-hospital mortality of AE-IPF is 27–65%, and 3-month mortality is 30–74% [28, 48–50], with a median survival of ∼3–4 months following the event. Mortality ranges from 55% to 96% in patients who receive mechanical ventilatory support [16, 51, 52]. The variable outcome estimates are partly due to the use of different diagnostic criteria and study designs, and additional studies are needed to clarify the impact of the revised AE-IPF definition and criteria on the outcomes of AE-IPF. Patients who survive an AE-IPF generally do not return to their previous baseline, indicating the importance of a clear discussion on patient and family expectations and the need to set appropriate goals of care.

The economic burden of AE-IPF is similarly high [53, 54], with many patients requiring prolonged admission to hospital and use of significant healthcare resources. A study based on the Spanish National Health System estimated that the average cost of AE-IPF was €11,666 per event [53]. Another study using a national commercial claims database in the USA suggested a similar average cost of USD14,731 per event [54]. These data demonstrate the high personal and societal impact of AE-IPF, and the need for additional studies evaluating preventative strategies and potential therapies.

 https://doi.org/10.1183/2312508X.10015916

Conclusion

AEs are unpredictable and important events in the natural course of IPF. The revised definition and diagnostic criteria for AE-IPF provide a more practical and evidence-based framework for clinicians and researchers that is designed to facilitate future studies of this condition. Future goals include determination of the incidence of AE-IPF in the antifibrotic era, identification of the pathobiological mechanisms of AE-IPF and the biological relevance of specific triggers, and evaluation of specific therapies that could prevent AE-IPF or improve outcomes. The increasing number of multicentre registries and networks will facilitate the cohort studies and clinical trials that are needed to address these and other research questions.

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Disclosures: K. Tanizawa worked for the Dept of Respiratory Care and Sleep Control Medicine at Kyoto University (Kyoto, Japan) until January 31, 2017. The department is funded by endowments from Philips Respironics, Teijin Pharma Ltd, Fukuda Denshi Inc. and Fukuda Lifetec Keiji. K. Tanizawa has received personal fees from ONO Pharmaceutical Co. Ltd, Kyowa Hakko Kirin Co. Ltd, Eizai Co. Ltd, Shionogi & Co. Ltd, Actelion Pharmaceutical Co. Ltd and MSD, outside the submitted work. H.R. Collard has received personal fees from Alkermes, aTyr Pharmaceuticals, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Global Blood Therapeutics, Genoa, ImmuneWorks, Moerae Matrix, Navitor, Parexel, Patara, Pharma Capital Partners, PharmAkea, Prometic, Takeda, Toray and Xfibra, outside the submitted work. C.J. Ryerson has received grants and personal fees from Boehringer Ingelheim and Hoffmann La Roche, outside the submitted work.

Chapter 6

Chemical air pollution and allergen exposure

Isabella Annesi-Maesano

Major threats causing AEs of pulmonary diseases include exposure to chemical air pollutants and biocontaminants, including allergens. The impact of chemical air pollutants on asthma attacks and COPD exacerbation is well established. The impact of airborne allergens is also well documented in the case of asthma and for rhinitis attacks and aggravation. Recently, an association has also been found between air pollution and IPF exacerbations. The modalities of action are different. The lag period (time between the exposure event and aggravation) is short (up to few hours or days) for both allergens and chemical air pollution in the case of asthma, and longer in the case of chemical pollutants for COPD and IPF. Whether a combination of air pollution and allergens is associated with a higher risk of pulmonary disease aggravation than exposure to each individually needs to be elucidated. The role of prevention has been promoted, but is often difficult in practice.

Cite as: Annesi-Maesano I. Chemical air pollution and allergen exposure. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 66–75 [https://doi.org/10.1183/2312508X.10016016].

Major threats causing AEs of pulmonary diseases include exposure to altered air quality provoked by chemical air pollutants and biocontaminants. Chemical air pollution may be due to anthropogenic emissions of air pollutants or to natural sources. In the last century, in terms of public health, the massive increase in emissions of chemical air pollutants due to economic and industrial growth has made air quality a major problem for a large number of countries worldwide. Vehicular pollution causes a decrease in air quality in cities of industrialised countries, whereas the industries themselves still constitute the most important source of air pollution in countries in the process of industrialisation. However, other anthropogenic sectors producing air pollution should not be underestimated worldwide, such as energy production and use, agriculture, commercial, institutional and households. The return to wood for heating in the last decade has provided another source of pollution, even in Europe. While wood fuel has an indisputable advantage in terms of greenhouse gas emissions and is considered a renewable energy, it is responsible for the emission of many other air pollutants, both gaseous and particulate, and has an impact on respiratory health [1]. In addition, desert sand, marine salt and volcanic

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ash, as well as other forms of natural pollution, add to the increasing levels of anthropogenic dust and gases that pollute the air. Climate change heavily affects ozone (O_3) and particle emissions [2, 3]. Climate change-related hot spells are responsible for O_3 production and increase morbidity and mortality, as observed during the summer of 2003 in Europe [3]. Particulate matter will increase because of urbanisation and natural phenomena such as wildfires and desertification. It has been estimated that, worldwide, 339 000 premature deaths per year on average are attributable to air pollution from wildfires, in particular to particulate matter [4]. At the same time, individuals are also exposed to air pollution inside premises, where they spend 80–90% of their time in industrialised countries.

Climate change has been shown to cause dramatic changes in the distribution of plants and moulds as a result of temperature and humidity variations, as well as flood intensifications [5]. The resulting phenomena of extended pollen season (overall of the most allergenic pollen species) and increased spore productivity and dispersion have led to higher allergen concentrations, and thus to an increase in the risk of asthma and rhinitis development and aggravation [6]. In addition, there exists a synergy between chemical air pollution on the one hand, and pollen and spore allergens on the other, leading to higher allergenicity [7]. No significant increase in recent decades in other airborne allergens related to respiratory allergic diseases, such as indoor house dust mites (HDMs) and pets, has been documented. However, it is possible that people currently have more contact with indoor allergens because of the increased insulation of buildings to enable energy savings.

Short-term health impact assessment

Our knowledge of the short-term impact of chemical air pollution and allergen exposure has increased enormously over the last 30 years due to the development of new statistical methods. Important among these methods are time series studies, which link chemical air pollutants or biocontaminant levels measured daily over months or years in a given geographical area with a temporal series of measurable health indicators, such as hospitalisation, emergency room visits, medical consultations and medication use, recorded on a daily basis in the same period and zone. Such analyses investigate whether there is a statistical association between exposure and health indicators, taking potential confounders of the relationship (*e.g.* age, sex, tobacco smoking, occupation) into account, and are based on various models. The advantage of such studies, made possible by existing databases, is that they relate to large population groups that have been monitored for often very prolonged periods of time. The statistical power of these studies is therefore considerable and makes it possible to highlight statistically significant risks even of extremely low amplitude. Other methods included the Cox proportional hazards model, generalised additive models and generalised estimated equations. Thus, in recent years, the literature has highlighted short-term health effects that have not been described previously. These are not new effects, but are effects that could not be determined previously using the available methods of study.

Short-term effects of allergen exposure

There is ample clinical evidence that attacks of asthma and allergic rhinitis can be triggered by indoor and outdoor allergens [8]. Indoor allergens include HDMs, moulds, pets,

cockroaches and rodents, while outdoor allergens are limited to pollens and moulds. Strong clinical observations support the independent role of HDM exposure in triggering asthma morbidity in terms of symptoms, medication use and emergency department visits [9, 10]. Less evidence exists for allergic rhinitis. Evidence of the relationship of moulds to asthma and allergic rhinitis in indoor air is well documented [11, 12]. More recent data also implicate their metabolic products, such as ergosterol and microbial volatile compounds [12]. Pets, such as dogs and especially cats, can trigger asthmatic symptoms in sensitised subjects [13]. The involvement of mouse and rat allergens in asthma morbidity at the population level is less well documented [14]. Cockroach allergens undoubtedly contribute to asthma morbidity [15]. Pollens are well known risk factors for hay fever [16]. Grass pollen count aggravated severe allergic rhinitis in terms of symptoms in a large sample, confirming the need for proper treatment and preventative measures in patients sensitised to grass pollen [17]. Pollen can also induce seasonal asthma in sensitised individuals. An increasing body of evidence has shown the occurrence of severe asthma epidemics during thunderstorms in the pollen season, in various geographical zones, in patients suffering from hay fever [18]. The main hypothesis explaining the association between thunderstorms and asthma claims that thunderstorms can concentrate pollen grains at ground level, which may then release allergenic particles of respirable size into the atmosphere after their rupture by osmotic shock (figure 1) [18]. Thunderstorm asthma may exist also for moulds [18]. Outdoor moulds can lead to severe asthma exacerbations [20].

Short-term effects of chemical air pollution exposure

Sources of chemical air pollution to which humans are exposed are both anthropogenic and natural (table 1). Indoor air quality is affected by cigarette smoke and by volatile

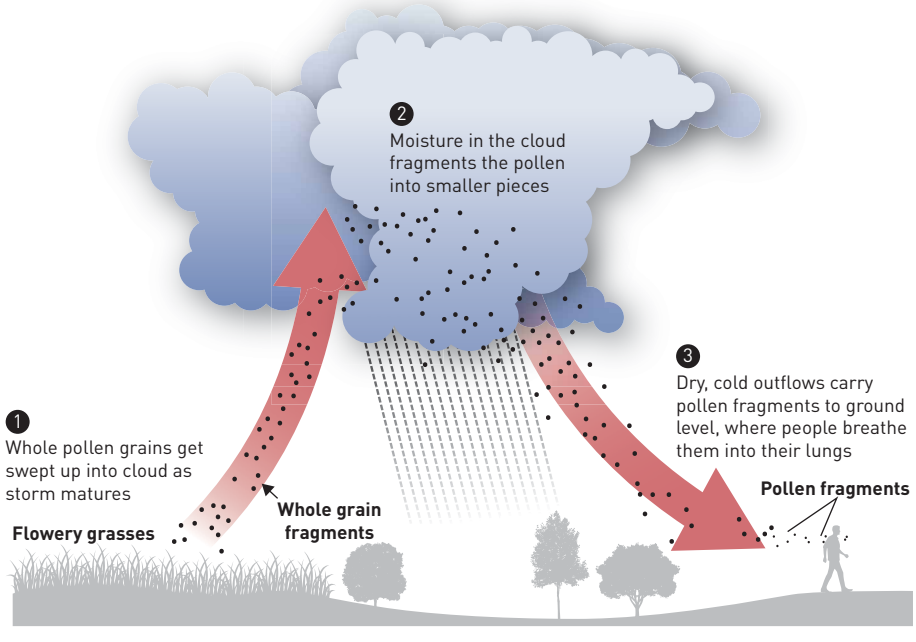
2
Moisture in the cloud fragments the pollen into smaller pieces
3
Dry, cold outflows carry pollen fragments to ground level, where people breathe them into their lungs
Pollen fragments
1
Whole pollen grains get swept up into cloud as storm matures
Flowery grasses
Whole grain fragments

Figure 1. Thunderstorm asthma: the case of pollen fragments. Reproduced and modified from [19], with kind permission of the figure's original artist, Alex Gonzalez.

https://doi.org/10.1183/2312508X.10016016

organic compounds, in the form of both gases and particulate matter, generated by building and cleaning materials. A cocktail of these allergenic and toxic pollutants can be formed from paints, glues, floor coverings, maintenance products, do-it-yourself products, heating appliances and gas cooking. Outdoor air pollution is due to traffic, industry and residential use.

Although there are now tens of thousands of proven or suspected air pollutants, sometimes acting in synergy with other parameters (*e.g.* temperature, wind), only a limited number are monitored routinely. At the urban level, these are sulfur dioxide (SO_2), O_3, oxides of nitrogen such as nitrogen dioxide (NO_2) and particulate matter.

In order of increasing severity, the short-term effects of chemical air pollution are respiratory symptoms, decreased respiratory function or infectious episodes in healthy subjects, and exacerbations of pre-existing respiratory diseases leading eventually to premature death.

Effects in the general population

At the population level, there is a correlation between variations in gaseous and particulate pollutants and an increase in respiratory symptoms, such as cough, wheezing,

Table 1. Indoor and outdoor chemical air pollutants and their sources

Air pollutant	Outdoor sources	Indoor sources
Sulfur dioxide (gas)	Anthropogenic combustion (especially in industrial processes) of coal and fuel oil; natural combustion (*e.g.* wildfires, volcanos)	Combustion and transfer from outside
Oxides of nitrogen (can be transformed into acid under the action of solar radiation)	Motor vehicles and combustion plants; natural combustion (*e.g.* wildfires, volcanos)	Nitrogen dioxide from gas appliances and heaters
Ozone (gas)	Transformation of oxides of nitrogen, carbon monoxide and hydrocarbons under the action of solar radiation	Transfer from outside
Carbon monoxide (gas)	Incomplete combustion from motor vehicles; natural combustion (*e.g.* wildfires, volcanos)	Incomplete combustion and transfer from the outside
Particulate matter (solid and/or liquid particles suspended in the air and classified according to size)	Combustion (both anthropogenic and natural); transport and industrial processes	Combustion (including smoke from cigarettes) and transfer from the outside
Volatile organic compounds, comprising several thousand gases from different chemical families (*e.g.* alcohols, ketones, hydrocarbons)	Combustion (both anthropogenic and natural); vegetation	Construction products, decorations, furnishings, combustion (including cigarette smoke), *etc.*

breathlessness and bronchitis, which may result in seeking medical advice (from physicians or at a hospital) or medication use [21]. The association is more pronounced in children [21]. Short-term exposure to outdoor air pollutants has also been associated with lower lung function among female nonsmokers [22], confirming a role for air pollution. The adverse effects persisted for longer durations up to 7 days at higher air pollutant levels [22]. In the field of infectious pathology, an increase in the incidence rates of rhinosinusitis, bronchitis, bronchiolitis with respiratory syncytial virus infection and pneumonia in children has been observed in relation to increased O_3 and particulate matter of 2.5 µm ($PM_{2.5}$) and 10 µm (PM_{10}) in diameter [23].

Exacerbations in patients with respiratory diseases

There are many studies in the literature on the short-term effects of air pollution in people with asthma, most of which have been performed in asthmatic children. All these studies have shown a statistical association between an increase in the daily concentration of air pollutants and the risk of exacerbations, most often assessed by the child's admission to the emergency department. Among the pollutants, all are associated with asthma morbidity, but the most often considered air pollutant is $PM_{2.5}$ [23, 24]. The increase in risk often occurs 24 h after the rise in air pollutant level. Regular treatment might balance the harmful effects of exposure to air pollutants [24]. A British study evaluated the respiratory function of people with asthma during a 2 h walk in London, in an area polluted with diesel fumes or in a green zone, and observed a decrease in spirometric values of around 6% for those in the polluted area [25]. A more pronounced fall was found in patients with moderate asthma compared with those with mild asthma [25]. Fewer studies have dealt with COPD. Variations in air pollutant concentrations influence symptoms, lung function impairment, and emergencies and hospital admissions in COPD patients, particularly in the elderly [26, 27]. Furthermore, increased O_3 and NO_2 exposure over the preceding 6 weeks was associated with an increased risk of AE of IPF, suggesting that air pollution may contribute to the development of this clinically meaningful event [28, 29]. The lag period was longer in the case of chemical pollutants for COPD and IPF (up to 10 days) than in the case of asthma (several hours) [7, 30]. The effect is modest, as indicated by a recent meta-analysis according to which air pollution was involved in only 1% of hospitalisations for COPD exacerbations in China and European Union countries and in 2% in the USA [30]. However, a recent study showed that hospitalisation for COPD exacerbation was not statistically related to air pollutant variations, after taking into account day-to-day temperature [31].

Mortality

In a global meta-analysis, the increase in mortality was found to be ~1% for a 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ [32]. In France, an increase in mortality of 1–3% occurred within 24–48 h of a peak of pollution [33]. The most at-risk population group for mortality is the elderly [33].

Environmental tobacco smoking is another form of air pollution that affects respiratory health [21, 22], particularly in the elderly [35]. Environmental tobacco smoking has been related to both asthma attacks and COPD exacerbations [34–37].

Mechanisms

Four main mechanisms have been identified that illustrate the impact of air pollution and allergens on respiratory health: oxidative stress, inflammation and remodelling of the

 https://doi.org/10.1183/2312508X.10016016

airways, and immunological mechanisms of facilitation of an allergic response [38]. However, these mechanisms are not independent of each other (figure 2). Pollen allergenicity is increased by chemical air pollution [3, 6], and inhalation of allergens such as pollen together with diesel particulate matter or gases such as O_3, NO_2 and SO_2 may promote the penetration of allergens or allergenic submicronic particles of respirable size through the bronchi [18] and induce asthma attacks [40]. In addition, whether a combination of air pollution and allergens is associated with a higher risk of asthma aggravation than exposure to each individually needs to be elucidated.

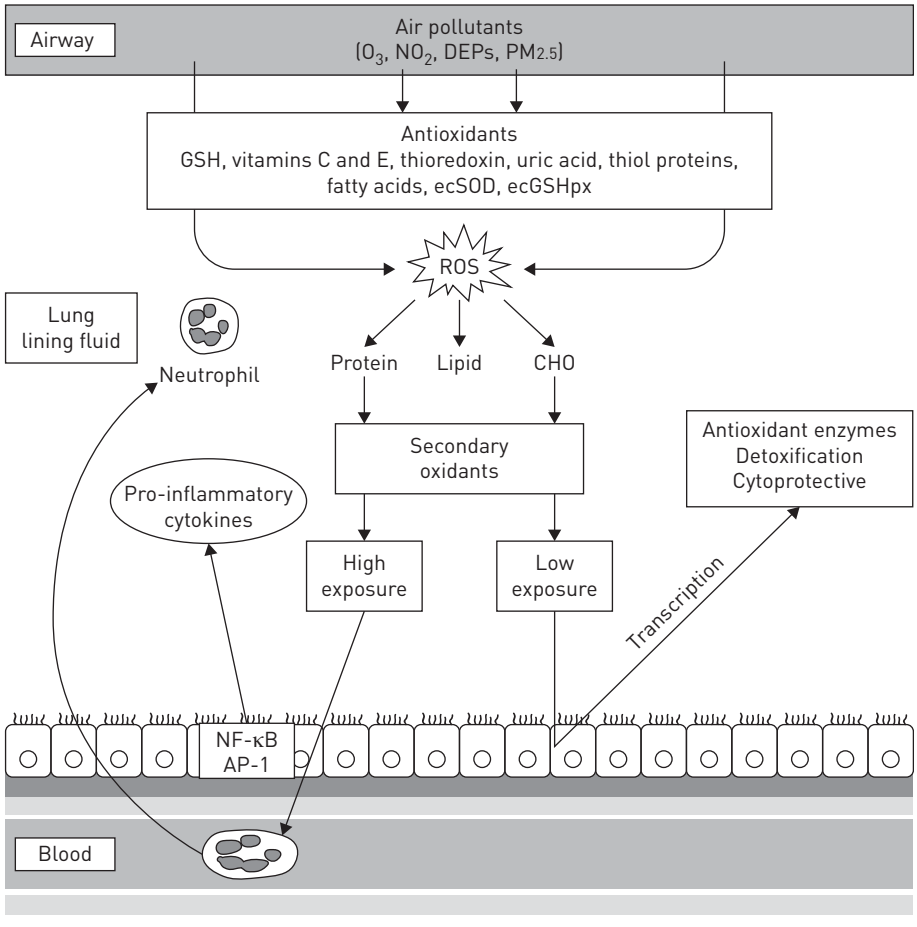

Figure 2. Oxidative stress and inflammation following air pollutant exposure, and underlying mechanisms. Reactive oxygen species (ROS) are chemically reactive species containing oxygen. Examples include peroxides, superoxide, hydroxyl radical and singlet oxygen. In a biological context, ROS are formed as a natural by-product of the normal metabolism of oxygen and have important roles in cell signalling and homeostasis. However, during times of environmental stress (*e.g.* exposure to air pollution), ROS levels can increase dramatically. This may result in significant damage to cell structures at different sites. Cumulatively, this is known as oxidative stress. ROS are also generated by exogenous sources. O_3: ozone; NO_2: nitrogen dioxide; DEP: diesel particle; $PM_{2.5}$: particulate matter of 2.5 μm diameter; GSH: glutathione; ecSOD: extracellular superoxide dismutase; ecGSHpx: extracellular glutathione peroxidase; CHO: carbohydrate; NF-κB: nuclear factor-κB; AP-1: activator protein 1. Reproduced and modified from [39] with permission.

Intervention and avoidance studies

Despite existing evidence of the impact of allergens on asthma and allergic rhinitis, avoidance studies are often not conclusive. Two types of effects have been evaluated: allergen levels and clinical effectiveness. In the case of HDMs and pets, the results are conflicting, with evidence obtained for some measures in terms of clinical effectiveness (*e.g.* washing bedding in a hot cycle, replacing carpets with hard flooring, use of acaricides, removing pets), but not for allergen levels according to expert committee reports or opinions and/or clinical experience of respected authorities [41]. Other measures (*e.g.* HDM allergen avoidance, high-efficiency particulate air filters) failed to show efficacy in either allergen diminution or clinical effectiveness [41]. Multifaceted remediation contributing to fungal allergen avoidance seems promising and should be promoted [42]. However, it is difficult to achieve in less affluent social classes [5]. One family out of every two has a pet in industrialised countries [43]. Surprisingly, this frequency is the same in families with at least one allergic member, which indicates that avoidance of pets is hard to achieve. In addition, allergic patients encounter pet allergens in many locations other than their home, because these allergens can be transported [44]. Environmental control of cockroaches and rodents can be achieved and leads to clinical benefit [41]. Avoidance of pollens and spores relies on minimising seasonal outdoor exposure and on preventing them from getting into the home [17]. It is likely that thunderstorms occurring during the pollen and spore proliferation season can cause thunderstorm asthma, so asthma patients should avoid being outside when they occur [18].

Avoidance of chemical air pollution exposure is not easy to achieve, as chemical pollutants are ubiquitous and may also have natural causes. At an urban level, clean air policies remain the most effective strategy. These are supported by results from different types of interventions to reduce air pollution. Most studies have highlighted a positive effect on respiratory indicators [45]. However, it is difficult to disentangle short-term from long-term effects. During the period of the Olympic Games in Beijing, when a citywide air pollution mitigation programme was undertaken, traffic and industrial emissions showed a significant decrease in biomarkers of inflammation, and amelioration of lung function and respiratory symptoms reductions were observed [46–50]. An intervention study on the impact of the change in use of wood stoves showed a decrease in the winter prevalence of respiratory symptoms and diseases in relation to decreased particle levels [51, 52]. A crossover study that examined the same subjects before and after the establishment of an area with traffic restriction yielded significant improvements in FVC observed among participants in the street where the air pollution showed the largest decrease [53]. A study in 2011 corresponded to a quasi-experimental situation. This was the temporary closure of a steel plant in Australia, which led to the diminution of respiratory admissions except in the case of COPD [54]. Reduction of air pollution emissions is also important to prevent long-term adverse effects of air pollution.

Lastly, it is well documented that the implementation of public smoking bans has led to a reduction in the hospitalisation of children with asthma [55].

Informing patients

It is the duty of the physician to inform his or her respiratory patients during air pollution peaks. These include patients with COPD, IPF and asthma, as well as infants, young

 https://doi.org/10.1183/2312508X.10016016

children and pregnant women to protect their offspring. The initial advice is to maintain strict observance of the patient's respiratory treatment. Respiratory patients undergoing treatment should follow their prescription and see whether symptoms appear (*e.g.* fatigue, sore throat, stuffy nose, cough, shortness of breath, wheezing, palpitations). The second recommendation to patients is to reduce intense physical and sporting activities (*i.e.* those that require breathing through the mouth because the nose is no longer sufficient). In the particular case of episodes of O_3 pollution, however, such physical and sporting activities can be maintained when they are practised indoors (because, for this particular pollutant, indoor concentrations are reduced compared with outdoor concentrations). There is no need to keep children at home in the event of a pollution peak, in particular because of the presence of domestic pollutants, especially passive smoking, but houses should not be naturally ventilated in the case of air pollution peaks. People who are identified as susceptible due to their age or health status should be subject to more restrictive counselling, for example restricting their travel in the vicinity of major roads at times of high traffic volume. As a general rule, physical activities involving strong ventilation (*e.g.* jogging) in the vicinity of heavily polluted roads is never a good idea for anyone, whether during a pollution peak or not. Lastly, it is recommended that individuals who suffer from allergies should protect themselves from pollen exposure during air pollution peaks [40] and at the beginning of thunderstorms [18].

Conclusion

Short-term effects of exposure to allergens are well documented and are important. Short-term effects of chemical air pollution are generally marginal compared with the long-term effects of air pollution. They consist of respiratory infections and symptoms (*e.g.* cough, wheezing, breathlessness) and exacerbations of asthma, COPD and IPF. Such exacerbations can lead to premature death. Overall, short-term effects have more importance for those with an increased socioeconomic burden. Children, the elderly and patients with respiratory diseases represent susceptible groups at increased risk of respiratory infections and symptoms. Other groups at higher risk of respiratory morbidity are those who are vulnerable because of higher exposure to air pollutants due to their socioeconomic position. An excess of respiratory mortality following a peak of air pollution is generally observed in patients suffering from chronic respiratory disease. Intervention studies indicate that reducing exposure corresponds to respiratory health improvement. However, other investigations are needed to better estimate the impact of air pollution.

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Disclosures: None declared.

Chapter 7

Viral infection

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Respiratory virus infections are the most common human infectious disease syndrome. Overwhelming epidemiological, clinical and experimental evidence indicates that respiratory viruses are the major triggers of AEs in patients with chronic airway diseases such as asthma, COPD, CF and interstitial lung disease. Nevertheless, treatments for respiratory viruses (other than influenza virus) have yet to be developed, and therefore the enormous burden of disease associated with respiratory virus infection in these chronic airway diseases remains unaddressed. This failure to develop antiviral therapies needs to be addressed by both the scientific community and the pharmaceutical industry if the morbidity and mortality of virus-induced exacerbations are to be reduced in the future.

Cite as: Ritchie AI, Mallia P, Johnston SL. Viral infection. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 76–96 [https://doi.org/10.1183/2312508X.10016116].

Viral infections of the respiratory tract constitute the commonest infectious disease syndrome in humans. The disease syndromes caused by respiratory viruses can vary from mild, predominantly upper respiratory syndromes, such as the common cold, to more severe lower respiratory disease (pneumonia, bronchiolitis), and are influenced by both the virus type and host factors, such as age. Although the severity of clinical disease varies, the vast majority of viral respiratory tract infections in healthy individuals result in mild symptoms lasting a few days and are self-limiting. However, when respiratory viruses infect individuals with chronic lung diseases, the consequences of infection are more severe. Respiratory infections in patients with chronic lung diseases such as asthma, COPD and CF result in more severe symptoms termed AEs. AEs are the major cause of morbidity, mortality and healthcare costs in these patients, and there is now extensive epidemiological, clinical and laboratory evidence that respiratory virus infections are major contributors to AEs. This chapter will review the role of respiratory virus infections in AEs of asthma, COPD, CF and interstitial lung disease (ILD).

Respiratory viruses

A wide range and variety of microorganisms can infect the human respiratory tract, with the commonest infectious agents being viruses. A large number of respiratory viruses infect

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the respiratory tract and cause a spectrum of clinical diseases ranging from mild, self-limiting upper respiratory tract symptoms (the common cold) to life-threatening lower respiratory syndromes, such as bronchiolitis and pneumonia. It was previously thought that individual viruses were associated with specific disease syndromes, for example rhinoviruses (RVs) with the common cold, respiratory syncytial virus (RSV) with bronchiolitis and influenza viruses with influenza-like illness. However, more recent studies using improved viral diagnostics have demonstrated that individual viruses can be detected in a range of clinical syndromes. For example, most episodes of "influenza-like illness" are actually associated with viruses other than influenza viruses [1, 2].

The most commonly detected viruses in upper respiratory tract infections are RVs. RVs are small, nonenveloped, single-stranded RNA viruses, members of the family *Picornaviridae* [3], and can be detected in 50–82% of common colds [4–6]. Children typically experience three to eight colds per year, while adults experience two to three episodes, and thus RVs are probably the most common infectious agent in humans. RVs are difficult to culture and therefore prior to the development of PCR-based diagnostic methods, their contribution to respiratory disease was underestimated. With the advent of PCR, it has become apparent that RVs are associated with a wider spectrum of disease severity than was previously appreciated and that they can cause more severe clinical illness, including pneumonia [7], otitis media [8] and bronchiolitis [9]. As will be discussed later, they are also the main virus detected in exacerbations of asthma and COPD. PCR has also led to the identification of a new RV species, RV-C, in addition to the previously identified RV-A and RV-B species [10]. RV-C is of particular clinical interest, as it may be associated with more severe illnesses compared with RV-A and RV-B [11].

Influenza viruses are perhaps the best characterised of all the respiratory viruses. Influenza viruses belong to the family *Orthomyxoviridae* and are classified into three types (A, B and C). Influenza A and B viruses cause seasonal epidemics, whereas influenza C virus generally causes mild disease. The clinical syndrome of influenza, or influenza-like illness, is characterised by symptoms such as fever, headache, myalgia and malaise, which are accompanied by the respiratory symptoms of cough, nasal discharge and sore throat. However, it is now known that there is considerable overlap in the clinical manifestations of different respiratory viruses, and other respiratory viruses are often detected in patients with a clinical diagnosis of influenza. A key feature of influenza viruses is their ability to undergo antigenic change and escape from immunity induced by previous infection and vaccination. Minor changes in surface antigens occur by the process of antigenic drift and result in seasonal epidemics. More dramatic changes in surface antigens can occur in influenza A viruses and are termed antigenic shift. When this occurs, it results in a novel virus strain to which a large proportion of the population does not have immunity and can therefore cause a global pandemic. There have been four pandemics in the past century, the most recent being the H1N1 swine flu pandemic in 2009 [12].

Second in importance to RVs as aetiological agents of the common cold are coronaviruses, which have also been identified in more severe clinical disease syndromes, although to a lesser extent than RVs [6–8]. However, recently a novel coronavirus was identified as the causative agent of the severe respiratory syndrome Middle East respiratory syndrome [13].

RSV is a member of the family *Paramyxoviridae* and has long been associated with bronchiolitis in infants. However, it is also a major cause of respiratory infection in the elderly, in whom it is associated with considerable morbidity and even mortality [14, 15], and with pneumonia [7].

The introduction of PCR diagnostics has not only increased the detection rates of previously identified viruses, but has also led to the discovery of previously unknown viruses that infect the respiratory tract. Two novel respiratory viruses that have been identified are human metapneumovirus (HMPV) and human bocavirus (HBoV) [16, 17]. These viruses have been detected in a wide range of respiratory infectious syndromes in both children and adults [18, 19]. Thus, there are numerous viruses that can infect the respiratory tract, and it is likely that further novel viruses will be discovered in the future. The recent identification of novel RVs and coronaviruses together with the discovery of novel viruses such as HMPV and HBoV highlight how our knowledge regarding both existing and novel respiratory viruses continues to evolve.

Asthma

Asthma has a global prevalence in excess of 300 million, making it a significant source of morbidity and mortality worldwide [20]. There is evidence that asthma prevalence has increased in recent decades, such that in many European countries up to 30% of children reported wheeze in the last year [21]. The pathogenesis of asthma is complex and varies across distinct clinical phenotypes. Complex interactions between genetic, epigenetic and environmental factors predispose patients to develop a limited number of dysfunctional immunological regulatory patterns, which in turn dictate the presentation of clinical phenotypes.

Asthma has a typical disease course of chronic respiratory symptoms, such as wheeze and breathlessness, punctuated by periods of symptom worsening, termed AEs [22]. AEs are significant events as they impair QoL and are the predominant cause of mortality. Moreover, they often necessitate unscheduled healthcare visits, treatment costs and hospitalisation [23]. Therefore, preventing exacerbations is a major, currently incompletely met, therapeutic goal. A crucial step towards this goal is the recognition that AEs are most commonly due to respiratory virus infection [24, 25].

Viral infections as aetiological causes for asthma AEs

Asthma is characterised by airway hyperresponsiveness with subsequent diffuse reversible airways obstruction, manifesting as wheeze, chest tightness, breathlessness and cough. Recent discoveries have led to the reclassification of asthma as a heterogeneous condition encompassing several endotypes. The classic pattern is that of T-helper (Th) 2-predominant inflammation, with characteristically elevated levels of airway eosinophils, IgE, mast cells and exhaled nitric oxide [26]. Three additional asthma endotypes are recognised: 1) adult-onset asthma with eosinophilia but an absence of allergic disease [27], 2) obesity-related asthma with minimal Th2 inflammation and 3) a group who also have little Th2 inflammation but notably have sputum neutrophilia and a Th17 response. Work is ongoing to precisely define these subpopulations to lead to more effective, targeted therapies.

It has long been recognised that viral respiratory tract infections trigger exacerbations of asthma in both adults and children, but early studies reported low detection rates of viruses in asthma exacerbations, casting doubt on this association [28, 29]. The development of highly sensitive and specific molecular diagnostic techniques using reverse transcriptase-PCR technology demonstrated the presence of viruses in 80–85% of asthma exacerbations in school-aged children and in ~80% of exacerbations in adults [24, 30–32], leading to a

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re-evaluation of the role of virus infections in asthma. Other viruses that are identified in asthma exacerbations include influenza viruses, RSV, coronaviruses and HPMV. Influenza virus infection is common during the winter, frequently emerging as a local or national epidemic. The 2009 H1N1 influenza A virus pandemic brought about a number of studies highlighting asthma as an important comorbidity in those infected [33]. Moreover, asthma was associated with increased disease severity, a higher risk of hospitalisation, the need for intensive care and overall mortality [34–36].

The response to viral infection differs between healthy and asthmatic individuals, as highlighted by a study of cohabiting partners, one of whom had asthma, which found that those with asthma exhibited significantly more severe and longer lasting lower respiratory symptoms and greater changes in airway physiology than those without asthma [37]. It was subsequently shown that experimental RV infection in asthmatic individuals precipitates AE, providing direct evidence for a causative role of RVs [38, 39]. Additionally, the inflammatory and symptomatic consequences of an RV infection are more severe in people with asthma than in those without. The demonstration that, following nasal inoculation, RV can infect bronchial epithelium provided a mechanism by which RV might trigger lower respiratory tract symptoms [40, 41]. Therefore, it follows that the balance between protective antiviral responses and inflammatory responses may be skewed in asthmatic individuals, which probably accounts for the differences in symptom duration and severity. Underpinning this is the airway epithelium, which is highly dynamic and orchestrates the immune, inflammatory and host defence response observed in both stable and exacerbated disease.

Immune response to RV infection

The majority of experimental work on epithelial responses in asthma has focused on RV infections, as this is the most commonly detected virus type during exacerbations in epidemiological studies [24, 25, 42].

RVs primarily enter and replicate in epithelial cells, triggering a cascade of immune and inflammatory responses and cytotoxicity (figure 1) [41, 43]. Human bronchial epithelial cells (HBECs) serve as the major host cell for virus replication [44], but other cells, including airway smooth muscle cells [41], fibroblasts [45] and alveolar macrophages [38], may also be important sites of infection, inducing inflammatory mediators [38, 46–48], although significant virus replication seems to be limited to epithelial cells [49].

Virus replication leads to synthesis of viral RNA, which is recognised by innate immune receptors. These pattern recognition receptors include the cytosolic RNA helicases, retinoic acid inducible gene I (RIG-I), melanoma differentiation-associated protein-5 (MDA-5), dsRNA/protein kinase receptor and Toll-like receptor (TLR)-3, -7 and -8 [50–53]. Following ligand and receptor binding, there is a signalling cascade, which leads to the activation of transcription factors including interferon (IFN) regulatory factor (IRF)-3 and -7, nuclear factor-κB, activating transcription factor 2 (ATF2) and c-Jun [49, 54, 55]. The activated transcription factors then translocate to the nucleus of HBECs to induce transcription of type I and type III IFNs (IFN-α/-β and IFN-λ1, -2 and -3, respectively) and many pro-inflammatory cytokines and chemokines including IL-6, IL-8 (also known as CXCL8), IL-16, epithelial-derived neutrophil-activating peptide 78 (ENA-78 or CXCL5), CCL5 (also known as RANTES) and IFN-γ-induced protein 10 kDa (IP-10 or CXCL10) [40, 56–63].

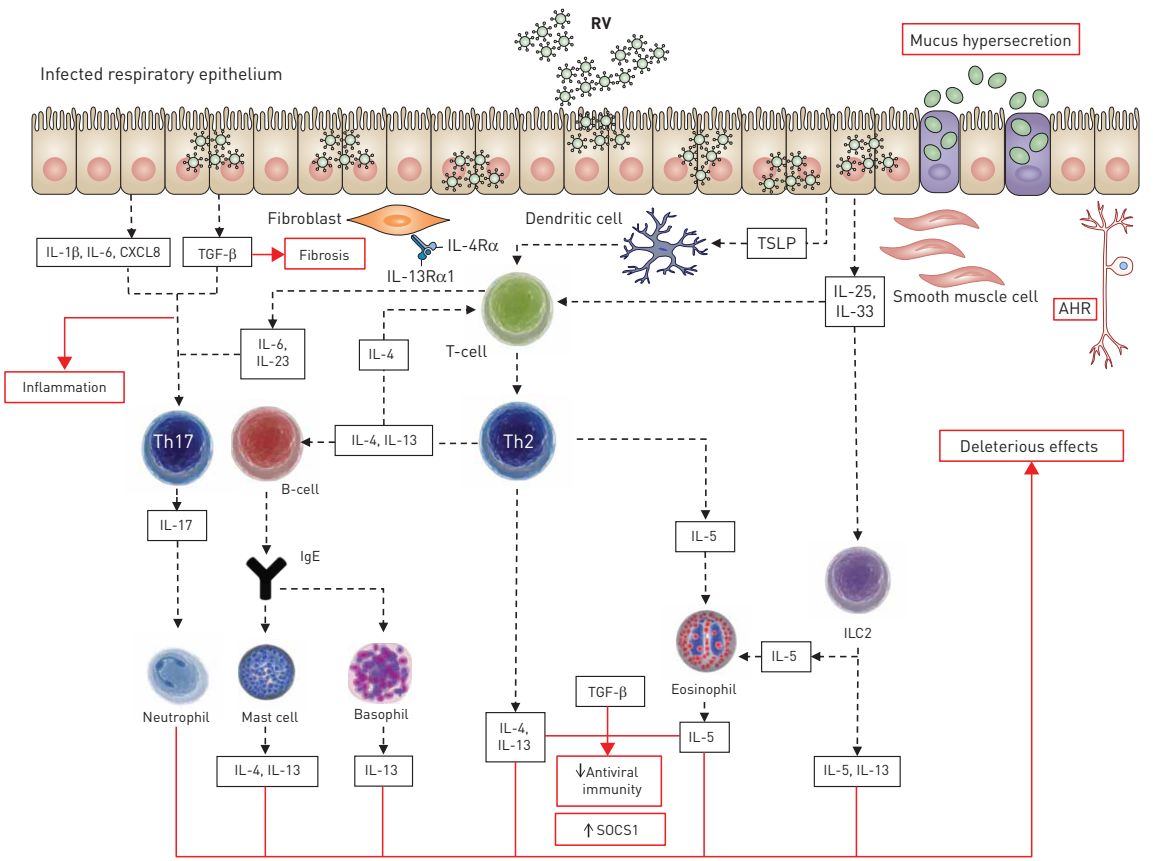

Figure 1. Schematic highlighting the airway epithelial response to rhinovirus (RV) infection in asthma. RV infection induces IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) in the asthmatic epithelium. This figure provides an overview of how the T-helper (Th) 2 pathway is induced by this process and drives the cardinal deleterious effects (highlighted in red boxes) in asthma. TGF-β: transforming growth factor-β; IL-4Rα: IL-4 receptor α; IL-13Rα1: IL-13 receptor α1; AHR: airway hyperresponsiveness; ILC2: type 2 innate lymphoid cell; SOCS1: suppressor of cytokine signalling 1.

https://doi.org/10.1183/2312508X.10016116

IFNs play a crucial role in the host immune response to viral infection [64]. Their antiviral effects occur directly through inhibition of virus replication in cells, and indirectly through stimulation of innate and adaptive immune responses. The direct antiviral activity of type I IFNs is brought about by a number of mechanisms, including blocking virus entry into cells, control of viral transcription, cleavage of RNA, blocking translation and induction of apoptosis [65]. These protective effects are mediated through the upregulation of IFN-stimulated genes and the production of antiviral proteins [64]. The indirect effect of IFNs is mediated through the induction of cytokines and chemokines, leading to recruitment of natural killer cells and $CD4^+$ and $CD8^+$ T-cells [66], upregulation of the expression of major histocompatibility complex I proteins on cells and upregulation of antigen-presenting cell co-stimulatory molecules. Therefore, a robust IFN response is central to effective antiviral responses and resolution of virus infection.

Abnormalities of immune responses associated with asthma

Deficient innate antiviral immunity

The first report to suggest impaired innate immune responses to virus infection in asthma emerged in 2002 when Bufe *et al.* [67] demonstrated significantly lower levels of virus-induced IFN-α in blood cultures of children with atopic asthma than in those people with nonatopic asthmatic and in healthy children (table 1). Following this, Wark *et al.* [68] harvested primary HBECs from normal and asthmatic subjects and showed that RV replication was increased in the cells from asthmatic subjects. Interestingly, they established that induction of IFN-β was both delayed and deficient in asthmatic subjects, and that administration of exogenous IFN-β resulted in induced apoptosis and reduced virus replication, demonstrating a causal link between deficient IFN-β and increased virus replication [68]. Restoration of the antiviral response with the administration of type I IFN was verified in subsequent work [84]. Our group has shown that there is impaired IFN-α and IFN-β production in the alveolar macrophages of asthmatic subjects [75]. Contoli *et al.* [61] studied atopic asthmatic subjects and similarly showed deficient IFN-λ production by HBECs and alveolar macrophages infected *ex vivo* with RV-16. This study induced asthma exacerbations through an experimental RV model to demonstrate that clinical measures of exacerbation severity were inversely proportional to IFN-λ generation [61].

However, not all studies have confirmed deficient IFN responses in asthma [85–88], although it should also be noted that the *in vitro* studies highlighted were small, with varying experimental conditions, such as the cell culture technique and virus doses used (table 2). Thus, although IFN deficiency is a plausible mechanism underlying the observed increased severity of virus infection in asthma, it has not been universally demonstrated. There are a number of reports suggesting a relationship between biomarkers of asthma/allergy severity and the scale of IFN responses [74–76, 93]. However, the magnitude of delayed/deficient IFN responses does not appear to correlate unanimously with the disease spectrum. Inhaled IFN-β has proceeded to a phase II RCT in persistent asthma (British Thoracic Society (BTS) guidelines, steps 2–5) at the onset of a naturally occurring viral infection [94]. The primary outcome of interest, a change in the Asthma Control Questionnaire-6 score from baseline to day 8, was not significantly different between the treatment and placebo arms. However, in a pre-specified subgroup analysis of patients with more severe disease (BTS guidelines, steps 4 and 5), inhaled IFN-β was effective in preventing a virus-induced increase of asthma symptoms, leading to the conclusion that studies of IFN-β should next target patients with moderate or severe disease [94]. It is also

Table 1. Studies supporting type I and/or type III interferon (IFN) deficiency in the asthmatic airway epithelium

First author [ref.]	Asthmatic subtype studied (*versus* healthy control unless stated)	Cell type	Stimulating virus/ analogue	Effect on IFN studied
Bufe [67]	Atopic children *versus* nonatopic asthmatic subjects and healthy children	Blood cultures	NDV	Decreased IFN-α (atopic asthma)
Wark [68]	Atopic asthmatic subjects	HBECs	RV	Decreased IFN-β
Contoli [61]	Atopic asthmatic subjects	HBECs and alveolar macrophages	RV	Decreased IFN-λ
Gehlhar [69]	Atopic asthmatic subjects	PBMCs	RSV and NDV	Decreased IFN-α
Gill [70]	Allergic asthmatic subjects	Plasmacytoid dendritic cells	Influenza A virus	Decreased IFN-α
Uller [71]	Asthma (GINA criteria); mild to severe disease studied	HBECs	dsRNA	Decreased IFN-β
Likura [72]	Atopic asthmatic subjects	PBMCs	RV	Decreased IFN-α
Forbes [73]	Pregnant women with asthma, asthmatic subjects and healthy controls	PBMCs	RV or TLR7 agonist	Decreased IFN-α and IFN-λ (during exacerbations); highly decreased IFN-λ (pregnant women with asthma)
Edwards [74]	Children with severe therapy resistant atopic asthma	HBECs	RV	Decreased IFN-β and IFN-λ
Sykes [75]	Atopic asthmatic subjects	BAL cells	RV	Decreased IFN-β
Baraldo [76]	Asthmatic subjects (atopic and nonatopic) and atopic nonasthmatic individuals	HBECs	RV	Decreased IFN-β and IFN-λ
Durrani [77]	Allergic asthmatic children *versus* nonasthmatic children and nonallergic nonasthmatic children	PBMCs	RV	Decreased IFN-α and IFN-λ
Zhu [78]	Primary tracheobronchial epithelial cells	Primary tracheobronchial epithelial cells	*Alternaria alternata*, RV, dsRNA	Decreased type I and type III IFN gene expression

Continued

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Table 1. Continued

First author [ref.]	Asthmatic subtype studied (*versus* healthy control unless stated)	Cell type	Stimulating virus/ analogue	Effect on IFN studied
Parsons [79]	Asthma (GINA criteria)	HBECs	RV	Decreased IFN-λ
Spann [80]	Children with wheeze and/or atopy	Nasal epithelial cells, tracheal epithelial cells	RSV	Decreased IFN-β
Wagener [81]	Allergic asthma with concomitant rhinitis and allergic rhinitis	Primary nasal and HBECs	dsRNA	Decrease in several IFN-related genes
Simpson [82]	Neutrophilic airway inflammation and eosinophilic (prescribed high doses of ICS)	PBMCs	RV	Decreased IFN-α and IFN-β
Rupani [83]	Severe, uncontrolled allergic asthma	BAL alveolar macrophages	RV	Decreased IFN-α and IFN-β

NDV: Newcastle disease virus; HBEC: human bronchial epithelial cell; RV: rhinovirus; PBMC: peripheral blood mononuclear cell; RSV: respiratory syncytial virus; GINA: Global Initiative for Asthma; TLR7: Toll-like receptor 7; BAL: bronchoalveolar lavage; ICS: inhaled corticosteroids.

possible that the exact nature of IFN deficiency relates to discrete asthma phenotypes. Further work is indicated in this area to understand these mechanisms, with a focus on larger subject numbers, careful patient selection and characterisation of distinct asthmatic endotypes. This was underlined by the recent cross-sectional study by da Silva *et al.* [92], who found that neutrophilic but not eosinophilic asthmatic subjects had increased IFN-β, IFN-λ1 and IFN-stimulated genes when clinically stable. This may represent activated innate immunity to increased bacterial burden in this asthma endotype, and serves to highlight this important point.

The mechanisms underpinning deficient innate IFN induction in asthma are of great current interest. Studies have strongly implicated IgE binding to its receptor on dendritic cells and peripheral blood mononuclear cells (PBMCs), and, upon being cross-linked, inhibition of IFN induction by viruses [70, 77]. An important recent study has confirmed previous reports that anti-IgE therapy substantially reduced exacerbation frequency, particularly in more severe asthma and in exacerbation-prone asthma in school-aged children [95]. Importantly, this study also reported that anti-IgE therapy was able to restore deficient innate antiviral immunity (IFN-α production in response to RV infection in IgE-cross-linked PBMCs) in these children with asthma, and that those children with better restoration of antiviral immunity had very substantial reductions in exacerbation frequency compared with children with less good restoration [95]. Further research is needed to understand the intracellular mechanisms involved in suppressing IFN induction following cross-linking of IgE bound to its receptor.

Another mechanism implicated in IFN deficiency in asthma is induction of suppressor of cytokine signalling (SOCS) 1 and SOCS3. SOCS1 and -2 are proteins known to function as

Table 2. Studies not supporting type I and/or III interferon (IFN) deficiency in the asthmatic airway epithelium

First author [ref.]	Asthmatic subtype studied	Cell type	Stimulating virus/ analogue	Effect on IFN studied
Lopez-Souza [86]	Allergic asthma	Nasal epithelial cells and HBECs	RV	No change in IFN-β
Bochkov [85]	Atopic asthmatic and atopic nonasthmatic subjects	HBECs	RV	No change in type I or type III IFN expression
Sykes [87]	Mild, well-controlled atopic asthma	HBECs	RV	No change in IFN-λ and to a lesser degree IFN-β
Patel [89]	Asthma (9 out of 11 recruits atopic)	HBECs	Influenza A virus and RSV	No change in type I or type III IFN expression; decreased IFN-λ (in response to RSV) and increased IFN-λ (in response to influenza virus) in asthmatic groups
Sykes [88]	Atopic asthma	HBECs and PBMCs	TLR agonist	No change in type I or type III IFN expression
Spann [90]	Children with wheeze and/or atopy	Tracheal epithelial cells	RSV or HMPV	No change in IFN-β or IFN-λ production
Herbert [91]	Human airway epithelial cells, co-cultured with/without IL-4 and IL-13	Human airway epithelial cells	Poly(I:C)	Increased mRNA for type III IFN
de Silva [92]	Neutrophillic and mild to severe atopic asthma	BAL alveolar macrophages	RV	Increased IFN-β, IFN-λ1 and ISGs (neutrophilic); no change in IFN-β, IFN-λ1 or ISGs (atopic)

HBEC: human bronchial epithelial cell; RV: rhinovirus; RSV: respiratory syncytial virus; PBMC: peripheral blood mononuclear cell; TLR: Toll-like receptor; HMPV: human metapneumovirus; poly(I:C): polyinosinic–polycytidylic acid; BAL: bronchoalveolar lavage; ISG: IFN-stimulated gene.

negative regulators of cytokines. In murine models, SOCS1 and -2 negatively feedback on Th2 immunity [96–99], while in humans a genetic polymorphism enhancing SOCS1 is associated with asthma [100], and T-cell SOCS3 mRNA levels are increased in patients with asthma [96]. Gielen *et al.* [101] reported that RV infection and Th2 and pro-inflammatory cytokines increased levels of SOCS1 and -3 mRNA in HBECs, while SOCS1, but not SOCS3, was increased in bronchial biopsies in patients with asthma. SOCS1 overexpression in HBECs directly inhibited IFN-β-induced and virus-induced

 https://doi.org/10.1183/2312508X.10016116

IFN-β and IFN-λ1 promoter activation, and nuclear localisation of SOCS1 was shown to be necessary for this inhibition to occur [101]. As SOCS1 inhibits virus-stimulated IFN induction, antagonism of SOCS1 is an attractive therapeutic target.

Transforming growth factor (TGF)-β is a cytokine of interest because it mediates suppression of both IFN-λ and IFN-β in primary HBECs from healthy subjects exposed to RV [102], and IFN-α and IFN-β in RV-infected fibroblasts [103]. Mathur *et al.* [104] further investigated the role of TGF-β-mediated IFN suppression by co-culturing RV-infected BEAS-2B (human bronchial epithelium) monolayers with eosinophils to demonstrate enhanced suppression of IFN induction. This finding supports the observation that airway eosinophilia is associated with an increased risk of exacerbation in asthma.

To investigate how commonly inhaled asthma treatments modulate innate antiviral immunity, PBMCs were infected with RV and pre-treated with budesonide with and without formoterol. Interestingly, reduced type I IFN induction was noted in budesonide-treated cells from both healthy and asthmatic donors [105]. An influenza A virus murine infection model supported this finding when it demonstrated more severe disease in the steroid-treated group, and interestingly went on to show that adjuvant IFN treatment markedly reduced glucocorticosteroid-amplified infections in human airway cells and in mouse lung [106]. A study in which 47 men were randomised to receive prednisone or placebo found higher mean viral titres in the steroid-treated group in experimental RV infections [107]. Interestingly, budesonide and formoterol can inhibit HBEC inflammatory responses *in vitro* without interfering with virus replication or production of IFNs. These effects could potentially explain the beneficial effects of budesonide/formoterol combination therapy in preventing RV-induced asthma exacerbations [108].

An alternative mechanism of IFN suppression is *via* Th2 cytokine induction. IL-13 induces IL-1 receptor-associated kinase M (IRAK-M). IRAK-M is overexpressed in the asthmatic airway, where it appears to enhance lung epithelial RV replication and autophagy, but importantly it inhibits RV-induced IFN-β and IFN-λ1 expression [109]. *In vitro*, recombinant IL-13 was found to suppress dsRNA-induced expression of IFN-λ in airway epithelial cells, while a Janus kinase inhibitor prevented the IL-13-mediated suppression [110]. Contoli *et al.* [111] examined the effect IL-4 and IL-13 on epithelial innate immunity by assessing IFN responses (IFN-β and IFN-λ1) in RV-infected HBECs and found that IFN deficiency was brought about by inhibition of TLR3 expression and IRF3 signalling.

Viral infection promotes a type 2 immune response

The mechanisms by which viral infections (which induce a type 1 immune response) have deleterious effect on the type 2 inflammatory milieu seen in asthma are debated. Jackson *et al.* [39], using a novel method of airway lining fluid sampling from the nose (nasosorption) and bronchus (bronchosorption) combined with low-volume protein detection methods, were able to demonstrate that the type 2 cytokines IL-4, IL-5 and IL-13 are all induced *in vivo* in asthmatic but not in normal subjects in an RV-induced exacerbation model. Furthermore, levels of IL-5 and IL-13 during infection correlated with exacerbation severity, suggesting that the induction of type 2 cytokines might be functionally important [39].

The role of the epithelium in promoting the type 2 immune response is emerging from animal studies, and the molecules implicated include thymic stromal lymphopoietin

(TSLP), IL-25 and IL-33. Until very recently, their relevance to human asthma exacerbations was unknown. Beale *et al.* [112] investigated the role of IL-25 in this context and found that RV-infected HBECs from asthmatic donors had greater IL-25 induction, which correlated with donor atopic status. Human IL-25 levels were induced by experimental RV infection *in vivo*, and expression was greater in asthmatic subjects at baseline and during infection [112]. In mice, RV infection also induced IL-25 and augmented allergen-induced IL-25, and blockade of the IL-25 receptor markedly suppressed many RV-induced exacerbation-specific responses, including type 2 cytokines and chemokines, mucus production, and recruitment of eosinophils, lymphocytes and neutrophils, IL-4$^+$ basophils and Th2 cells, as well as type 2 innate lymphoid (ILC2) cells [112]. Therefore, asthmatic epithelial cells have an increased intrinsic capacity for IL-25 expression in response to a viral infection, and IL-25 is a key mediator of RV-induced exacerbations of pulmonary inflammation [112].

More recently, IL-33 has been identified as an inducer of type 2 inflammation [39]. IL-33 is induced by RV in the asthmatic airway *in vivo*, and IL-33 levels in asthmatic subjects were related to asthma exacerbation severity in a human experimental RV model [39]. Furthermore, induction of IL-33 correlated with viral load and levels of IL-5 and IL-13 brought about by infection [39]. *In vitro*, RV infection of primary HBECs strongly induced IL-33, and culture of human T-cells and ILC2 cells with supernatants of RV-infected HBECs (but not with supernatants of mock-infected HBECs) strongly induced type 2 cytokines (IL-4, IL-5 and IL-13 in T-cells, and IL-5 and IL-13 in ILC2 cells) [39]. These inductions were entirely dependent on IL-33, as blocking the IL-33 receptor in these co-cultures completely suppressed the inductions observed in the cultures with supernatants of RV-infected HBECs. Thus, virus-induced IL-33 released from HBECs and IL-33-responsive T-cells and ILC2 cells are key mechanistic links between viral infection and exacerbation of asthma [39].

In summary, evidence is accumulating to show that the immune responses to viral infection are impaired in asthmatic patients, and this probably underlies the increased disease severity following viral infection in patients with asthma. Further work is crucially needed to determine whether these impairments are common to all asthmatic subjects or whether they are characteristic of distinct phenotypes. A novel pathway has been identified, in which IL-25 and IL-33 and their receptors appear to be exciting new targets for the development of novel therapies for asthma exacerbations.

Chronic obstructive pulmonary disease

For decades, the main cause of COPD exacerbations was considered to be bacterial infection, and this belief is reflected in the continued extensive use of antibiotics in COPD exacerbations, despite weak evidence of their benefit [113]. Earlier studies using diagnostic techniques such as culture detected viral infections in a minority of COPD exacerbations, resulting in the focus on bacteria. However, with the advent of PCR-based diagnostic methods with much greater sensitivity for virus detection, the role of viral infections in COPD exacerbations was re-evaluated. Using PCR, respiratory viruses can be detected in 40–60% of COPD exacerbations [114–116]. The most frequently identified viruses are those that most commonly infect the human respiratory tract in healthy individuals and include RVs, influenza viruses, RSV and coronaviruses. Viruses can be detected in mild exacerbations treated in the community [117], in hospitalised patients [115, 118] and in

 https://doi.org/10.1183/2312508X.10016116

very severe exacerbations requiring admission to the ICU [119]. Viral infection rates are higher in exacerbated COPD patients compared with stable patients [117, 120–127]. These observations provide evidence for a causal relationship, but cannot exclude secondary causation (*i.e.* a nonviral aetiological agent of a COPD exacerbation (*e.g.* bacterial infection, air pollution) also increases susceptibility to viral infection). Our group has adopted a novel approach to investigating the association between viral infection and COPD exacerbations by carrying out experimental infection studies using RV in COPD subjects. In these studies, COPD subjects were infected with RV and clinical samples were collected prior to and after inoculation [128–130]. Overall, 95% of successfully infected subjects developed an AE of their COPD. We demonstrated that virus was present in the upper respiratory tract prior to progressing to the lower airway and causing COPD exacerbation onset, thereby excluding secondary causation [128–130]. Moreover, a temporal relationship between viral replication in the airways and exacerbation onset, and viral clearance and exacerbation resolution could be clearly demonstrated. Virus load correlated with markers of inflammation and oxidative and nitrosative stress in the airways [128, 129]. Therefore, these studies have provided novel evidence that for the first time directly link respiratory virus infection to COPD exacerbations.

Mechanisms of exacerbation induction by respiratory viruses

The mechanisms linking viral infection to COPD exacerbations have been studied much less intensively in COPD than in asthma. Consequently, much less is known about the mechanisms whereby respiratory viruses induce AEs in COPD patients.

Airway inflammation

The inflammatory response to viral infection has not been well characterised. In naturally occurring virus-induced COPD exacerbations, the few studies available have suggested a role for inflammatory cells such as neutrophils and eosinophils [124] and for inflammatory mediators such as IL-8/CXCL8, IP-10/CXCL10 and CCL5/RANTES [126, 131, 132]. Studies from experimental infection studies have indicated that RV infection induces airway neutrophilic inflammation and innate inflammatory meditators such as IL-1β, granulocyte–macrophage colony-stimulating factor, IL-8/CXCL8 and TNF-α [128, 129, 133]. In addition, we demonstrated that viral infection strongly induces markers of oxidative and nitrosative stress in COPD patients [128]. Moreover, these mediators are not induced in non-COPD subjects infected with RV [128]. These and other *in vitro* studies [134] indicate that the inflammation induced in response to viral infection is enhanced in COPD subjects, and this may be one mechanism whereby viruses induce exacerbations.

Impaired antiviral immunity in COPD

As described in a previous section, impaired production of IFNs in asthma may increase susceptibility to viral infection. In experimental RV infection studies in COPD, virus load was higher in COPD subjects compared with non-COPD subjects [128, 129]. As all subjects were inoculated with the same virus dose, this suggests that the mechanisms controlling viral replication are defective in COPD. When macrophages are stimulated *ex vivo* with RV, macrophages from COPD subjects produce less IFN compared with non-COPD subjects [129]. However, *in vitro* studies have had conflicting results, with similar [135] and even increased [134] IFN production reported in cells obtained from COPD subjects. In a murine model of COPD, IFN-α and IFN-β responses in response to viral infection were reported to be deficient in one study and virus clearance was impaired

[136], whereas another study reported reduced IFN-λ but not IFN-β, and no difference in virus load [137]. Therefore, it remains unclear whether production of IFN in response to viral infection is impaired in COPD patients.

Viral/bacterial co-infection in COPD exacerbations

Both viral and bacterial infections are common in COPD exacerbations, but studies appear to indicate that dual viral/bacterial infection does not play a major role in COPD exacerbations, with low detection rates ranging from 6.5% [119] to at most 27% [115, 124, 138]. However, one study reported that exacerbations are more severe with dual infection [124]. In experimental RV infections, secondary bacterial infections were detected in 60% of COPD patients successfully infected with RV [139]. Viruses and bacteria were detected at different time points, with viral infection occurring first and bacterial infection later, suggesting that studies of naturally occurring exacerbations that collect samples at a single time point underestimate the true incidence of dual infection [139]. This was confirmed in a subsequent study of naturally occurring exacerbations in which patients were sampled at two time points during an exacerbation [140]. In patients in whom RV was initially detected but bacteria were absent, 73% had bacteria detected when sampled again at day 14. There is evidence that dual viral/bacterial infection contributes to exacerbation severity. In COPD patients with *Haemophilus influenzae* detected in an exacerbation, the presence of a symptomatic cold was associated with higher bacterial loads [141], and in hospitalised patients with COPD exacerbations, dual viral/bacterial infection was associated with impaired lung function and longer hospital stays [124]. In experimental RV infection, co-infection was associated with prolonged lower respiratory symptoms [139]. Therefore, the role of dual viral/bacterial infections in COPD exacerbations is likely to have been overlooked and may be a factor contributing to the severity of COPD exacerbations.

Cystic fibrosis

CF is a common, autosomal-recessive genetic disorder caused by a defective function of the CF transmembrane conductance regulator protein. Pulmonary involvement is the most prominent manifestation of the disease. Respiratory infections are the leading cause of AEs, resulting in morbidity, a decline in lung function and hospitalisation. The major cause of infectious complications in CF has historically been considered to be bacterial infection, with *Pseudomonas aeruginosa* the most common organism detected. There is relatively little published work on the role of viral infections in CF, but recent studies suggest that viruses have a significant impact on this group of patients. The role of respiratory viruses is likely to have been significantly underestimated in the past. Older studies relied on serology, culture and immunofluorescence to implicate a viral cause in 10–28% of exacerbations in CF patients [142–145]. However, utilising modern PCR techniques, viruses were detected in 46% of patients with exacerbations of CF, compared with only 18% of patients in a stable condition [146]. Moreover, RV has been identified in 13–58% of CF patients with acute respiratory illness and was associated with increased respiratory symptoms, worse airway function and secondary bacterial infection compared with uninfected patients [144, 146–148]. A number of different viral species have been detected in CF patients, with the most common being RVs, influenza viruses and RSV. The incidence of viral infections in children with CF is not elevated in comparison with healthy children, but the severity of clinical illness associated with infection is demonstrably greater [149]. As with airways disease, viral infections are associated with a decline in lung

 https://doi.org/10.1183/2312508X.10016116

function and more severe clinical illness, indicating that they contribute to disease progression, and thus demonstrating the important need for further research in this field.

The mechanisms of virus-induced CF exacerbations and increased clinical illness are poorly understood, with conflicting results from published studies. Some authors have reported increased production of pro-inflammatory cytokines and chemokines by epithelial cells obtained from CF patients compared with healthy controls [149, 150]. However, others have failed to detect any differences in the cytokine profile of CF and normal cells [151, 152]. It remains unclear what leads to these conflicting observations. It is possible that the CF epithelium is intrinsically pro-inflammatory or that there is an inherent deficiency in antiviral innate immune responses in CF cells. Work in support of the latter hypothesis demonstrated increased replication following human parainfluenza virus infection of CF cells with correction by subsequent administration of IFN-α [149]. IFN responses were not impaired, but induction of nitric oxide synthase 2 (NOS2) was impaired in CF. NOS2 is required for the production of nitric oxide, which has potent antiviral effects, and therefore impaired nitric oxide synthesis may be one mechanism of impaired antiviral host responses in CF. Holtzman *et al.* [153] hypothesised that "hypersusceptibility" to viral infection *via* defective IFN pathways is a unifying pathway in asthma, COPD and now CF.

Interstitial lung disease

As in asthma, COPD and CF, ILD is characterised by stable periods punctuated by AEs, associated with a stepwise decline in lung function [154]. It is still possible that a proportion of these reflect the sequelae of infection that cannot be detected due to late presentation and limited microbiological methods, but studies of naturally occurring exacerbations have concluded that viruses account for only a small number [155–157].

Pulmonary infections are over four times as frequent in ILD, although it is unclear how many of these are viral [158]. Moreover, community-acquired pneumonia (both viral and bacterial) is associated with a higher mortality in ILD than in otherwise healthy controls [159]. How much of this is due to an impaired immune response arising from the ILD itself *versus* the immunosuppressive treatment that many of these patients are given (*e.g.* steroids) is difficult to delineate. Research into ILDs is further complicated by the heterogeneity of these disorders and the relatively imprecise diagnostic criteria.

The study of familial IPF has identified one way in which antiviral immunity can be affected in ILD. Genetic studies in six affected families identified a gene, *ELMOD2* [160], that has since been shown to be important in type I and type III IFN induction in response to TLR3 activation [161], which is part of the innate immune response to viruses.

That viral infections might be important in disease progression has been assessed further by small trials of antiviral therapy. However, studies to date have been significantly limited by small sample size, the lack of a control group and open-label designs, making it difficult to draw conclusions [162, 163]. Further studies are warranted, particularly given the paucity of effective treatments for IPF.

Chronic viral infection has been implicated in the pathogenesis of some ILDs, such as Epstein–Barr virus, cytomegalovirus, human herpesviruses 7 and 8, and hepatitis C virus. Advocates hypothesise that chronic and/or recurrent viral infection induces alveolar endothelial cell injury, in turn triggering the release of pro-inflammatory molecules that

bring about the disease pathology. This literature is beyond the scope of this *Monograph* and has been reviewed by Molyneaux *et al.* [164].

Conclusion

Respiratory virus infections are the most common infectious disease syndrome in humans. There is now overwhelming epidemiological, clinical and experimental evidence that respiratory viruses are the major triggers of AEs in patients with chronic airway diseases. Despite this, treatments for respiratory viruses (other than for influenza) have yet to be developed, and therefore the enormous burden of disease associated with respiratory virus infection in asthma, COPD and CF remains unaddressed. This failure to develop antiviral therapies needs to be addressed by both the scientific community and the pharmaceutical industry if the morbidity and mortality of virus-induced exacerbations is to be reduced in the future.

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Disclosures: S.L. Johnston has received personal fees from and is the co-owner of a patent at Sanofi Pasteur. He has received consultant compensation from Aviragen. He is the Director of and a shareholder at Therapeutic Frontiers. S.L. Johnston has received institutional funding and consultant compensation from Centocor, GSK, Chiesi, Boehringer Ingelheim, Novartis and Synairgen. He is also a shareholder at Synairgen. S.L. Johnston holds the following licensed patents. 1) Blair ED, Killington RA, Rowlands DJ, Clarke NJ, Johnston SL. Transgenic animal models of HRV with human ICAM-1 sequences. UK patent application no. 02 167 29.4, July 18, 2002, and international patent application no. PCT/EP2003/007939, July 17, 2003. 2) Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases. UK patent application no. GB 0405634.7, March 12, 2004. 3) Wark PA, Johnston SL, Holgate ST, Davies DE. Interferon-beta for anti-virus therapy for respiratory diseases. International patent application no. PCT/GB05/50031, March 12, 2004. 4) Wark PA, Johnston SL, Holgate ST, Davies DE. The use of interferon lambda for the treatment and prevention of virally-induced exacerbation in asthma and chronic pulmonary obstructive disease. UK patent application no. 0518425.4, September 9, 2005. 5) Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases. US patent application 11/517.763, patent no. 7569216, national phase of PCT/GB2005/050031, August 4, 2009. 6) Wark PA, Johnston SL, Holgate ST, Davies DE. Interferon-beta for anti-virus therapy for respiratory diseases. European patent no. 1734987, May 5, 2010. 7) Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases (IFNb therapy). Hong Kong patent no. 1097181, August 31, 2010. 8) Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases (IFNb therapy). Japanese patent no. 4807526, August 26, 2011. 9) Wark PA, Johnston SL, Holgate ST, Davies DE. Interferon-beta for anti-virus therapy for respiratory diseases. New Hong Kong, divisional patent application no. 11100187.0, January 10, 2011. S.L. Johnston also has the following patent pending: Burdin N, Almond J, Lecouturieir V, Girerd-Chambaz Y, Guy B, Bartlett N, Walton R, McLean G, Glanville N, Johnston SL. Induction of cross-reactive cellular response against rhinovirus antigens. European patent no. 13305152, April 4, 2013.

 https://doi.org/10.1183/2312508X.10016116

Chapter 8

Bacterial infection

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There is a wide range in the importance of bacteria as a trigger of exacerbations of respiratory disease, from a limited role in asthma and IPF to a dominant role in CF and bronchiectasis, with an intermediate role in COPD. Conventional techniques to understand bacterial infection, such as culture and antibody response studies, are being replaced with new methods, such as microbiome and immuno-inflammatory profiling, with consequent new insights and a rethinking of traditional concepts. The trend is towards recognition of a more substantial role for bacteria in exacerbations and even in stable disease pathogenesis than previously thought, with an appreciation that infections are often polymicrobial and that changes in microbial community composition can cause disruption of the stable homeostatic state leading to exacerbations. Future studies are likely to contribute further changes to our understanding in this area, with innovative therapeutic implications.

Cite as: Provost KA, Frederick CA, Sethi S. Bacterial infection. *In*: Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 97–113 [https://doi.org/10.1183/2312508X.10016216].

There is substantial variability in the role of bacteria as a cause of exacerbations in the respiratory diseases discussed in this *Monograph*. CF and non-CF bronchiectasis (NCFB) are bacteria-dominated diseases, and exacerbations in these diseases are often attributable to bacterial infection and improve clinically with antibiotics. At the other extreme, exacerbations of asthma and IPF have little evidence to support a bacterial causation, although antibiotics are often used in their treatment. Bacteria have an intermediate role in COPD where, after years of confusion and contradictory data, it has now become apparent that bacteria cause a substantial proportion of exacerbations, although accurate identification of these episodes remains a clinical challenge [1].

Evidence for a bacterial cause of a respiratory exacerbation can come from different sources. The classical approach is detection of a bacterial pathogen in culture from a respiratory sample at the time of the exacerbation. Such evidence is adequate to prove bacterial causation if the sample was obtainable from a sterile body site by a method that avoids contamination, for example a pathogen grown in culture from a properly obtained pleural fluid sample from a patient with empyema. However, the most common respiratory

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

samples obtained during exacerbations of these respiratory diseases are sputum samples. Attributing causation to a bacterial pathogen isolated from such a sample is problematic for two main reasons. Contamination of the sample from the upper airway (above the glottis), which is normally heavily colonised with bacteria, is common and introduces uncertainty as to the source of the isolated pathogen and whether it is really from the lung. The second confounding problem is that, in several respiratory diseases, including CF, NCFB and COPD, chronic "colonisation" of the lower airways is prevalent. This introduces additional uncertainty as to whether the isolated pathogen is a chronic coloniser that was resident in the lower airway before the exacerbation occurred, or whether it has acutely infected the lower airways and caused the exacerbation.

Another important line of evidence of bacterial causation of respiratory exacerbations is the development of a specific immune response to the bacterial pathogen. Reliable serological evidence of infection requires baseline samples prior to exacerbation, post-exacerbation samples collected after enough time has elapsed for the immune response to develop and use of the infecting (homologous) strain as an antigen in the immunoassay [2]. If these conditions are not met, immune response results are confounded by the presence of cross-reactive antigenic epitopes among bacterial strains and species, often resulting in contradictory and inconclusive results.

Bacterial infection induces a neutrophilic inflammatory response systemically and at a mucosal level. Inflammatory cytokines and chemokines that mediate such a response, including IL-17, IL-6, IL-8 and TNF-α as well as acute-phase reactants such as serum CRP and procalcitonin, would also be elevated in a bacterial infection. Studies of mucosal and systemic inflammatory patterns can therefore be used to indicate bacterial causation.

Finally, because bacterial infection is treatable with antibiotics, evidence of therapeutic benefit with antibiotic use for a respiratory exacerbation is supportive of bacterial causation.

Our understanding of the role of bacteria in human health and disease is undergoing a radical transformation with the advent of nonculture-based techniques to detect bacterial pathogens [3]. These microbiome techniques can determine the entire population of bacteria at a body site or in a sample, which is known as the microbiota. Exacerbations of several respiratory diseases discussed in this *Monograph* have been explored using such microbiome techniques with interesting results.

In this chapter, we will explore what conventional lines of evidence have shown about the role of bacteria in exacerbations in each of these respiratory diseases. The predominant bacterial pathogens implicated will then be discussed, followed by the new knowledge being generated by microbiome studies.

Chronic obstructive pulmonary disease

Acute infection in COPD is clinically recognised either as an exacerbation or as an episode of pneumonia. Accurate differentiation between the two presentations requires chest imaging, with the presence (pneumonia) or absence (exacerbation) of lung parenchymal involvement. Chest radiographs are most commonly used to make this differentiation, although they have limited diagnostic accuracy compared with CT scans [4]. Although pneumonia is generally considered as a more significant acute infection, exacerbations occur with much greater

 https://doi.org/10.1183/2312508X.10016216

frequency (at least 10-fold more) and have short- and long-term consequences that are as serious. The last two decades have seen a resurgent emphasis on the management and prevention of exacerbations of COPD, as data have accumulated showing that exacerbations are not mere "chest colds" but major contributors to decreases in QoL and lung function in COPD and to increased healthcare costs associated with this disease.

Aetiology and pathogenesis of COPD exacerbations

Exacerbations of COPD are airway inflammatory events that are induced by infection in the vast majority (~80%) of instances. These acute inflammatory events are superimposed on the chronic inflammation that is characteristic of COPD [5, 6]. Several studies have now shown that a variety of immuno-inflammatory cells and molecules are elevated during exacerbations in respiratory samples, including exhaled breath, sputum, bronchoalveolar lavage and bronchial biopsy [5–7]. Furthermore, systemic inflammation, measured by biomarkers such as CRP, has been described during exacerbations [7]. Of note, fever is an uncommon manifestation of exacerbations, seen in <20% of episodes, and, somewhat paradoxically, is an indicator of a viral rather than a bacterial exacerbation [8].

A normal tracheobronchial tree has redundant multifaceted innate defence mechanisms to maintain relative sterility in the face of repeated exposure to microbial pathogens by inhalation and microaspiration [9]. The structural and functional damage from smoke inhalation and the consequent inflammation appear to compromise several of these innate defence mechanisms, so that the usual transient bacterial flora can establish a foothold and proliferate in the lower airways. An immuno-inflammatory response that attempts to clear these proliferating microbial pathogens is associated with increased airway secretions, bronchospasm and mucosal oedema, which in turn worsen ventilation–perfusion mismatch and hyperinflation. The clinical manifestation of these pathophysiological changes is the classic cardinal symptoms of an exacerbation: new onset of or worsening of dyspnoea, cough, sputum production and sputum purulence [10]. Although predominantly an airway process, there are systemic effects, resulting in the fever and fatigue that often accompany exacerbations.

The aggravating infection can be viral, bacterial or a combination of both. Noninfectious factors are poorly understood, but include eosinophilic inflammation and environmental pollution [11]. Considerable overlap between different aetiologies has become apparent from recent studies where all causes were assessed simultaneously [6, 11]. The best current estimate is that 50% of exacerbations have a bacterial cause, in isolation or in combination with other causes, most commonly a preceding viral infection.

Conventional studies of bacterial infection in exacerbations

Although bacteria are isolated from sputum in 40–60% of exacerbations of COPD, their causative role remained controversial for decades [1, 12]. Although clinically the course of exacerbations was consistent with an acute infection, and exacerbations appeared to respond to antibiotic treatment, the actual evidence supporting a causative role of the isolated bacterial pathogens was scant and contradictory. Because chronic colonisation of the lower airway by bacteria in COPD was recognised, several sputum bacteriology studies were performed with the hypothesis that bacteria will be isolated more frequently or in increased numbers during exacerbations than during the stable state. However, these studies

did not support this hypothesis, casting doubt on the role of bacteria in exacerbations [13]. Immune studies were performed with the expectation of development of specific responses to bacteria following exacerbations. However, because these studies often used laboratory (heterologous) strains, and thus failed to account for the variability in antigenic structure among bacterial strains, their results were confusing and contradictory [14]. Placebo-controlled antibiotic trials in COPD exacerbations were small, with several additional design limitations, such as selection of patients and end-points, with consequent inconsistent results [2]. The scepticism regarding the role of bacteria in exacerbations of COPD was indeed well founded [12].

New findings on bacterial causation of exacerbations of COPD

Since the 1990s, several investigations that examined bacterial infection during COPD exacerbations with newer molecular, immunological and inflammatory techniques have been published [1]. Additional antibiotic trials that were better designed were also conducted [15, 16]. These investigations overcame the limitations of conventional methods, and have led to a new model of bacterial exacerbation pathogenesis in COPD that is now widely accepted (figure 1) [1]. Acquisition of new strains from the environment of nontypeable *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa* appears to be the predominant initiating event for a bacterial exacerbation of COPD [18]. In the absence of lung disease such as COPD, these pathogens colonise the upper respiratory tract, their natural ecological niche, and rarely cause disease. Microaspiration of upper airway secretions, which normally occurs during sleep and inhalation, is a route by which these bacteria gain ingress to the lower respiratory tract. In a

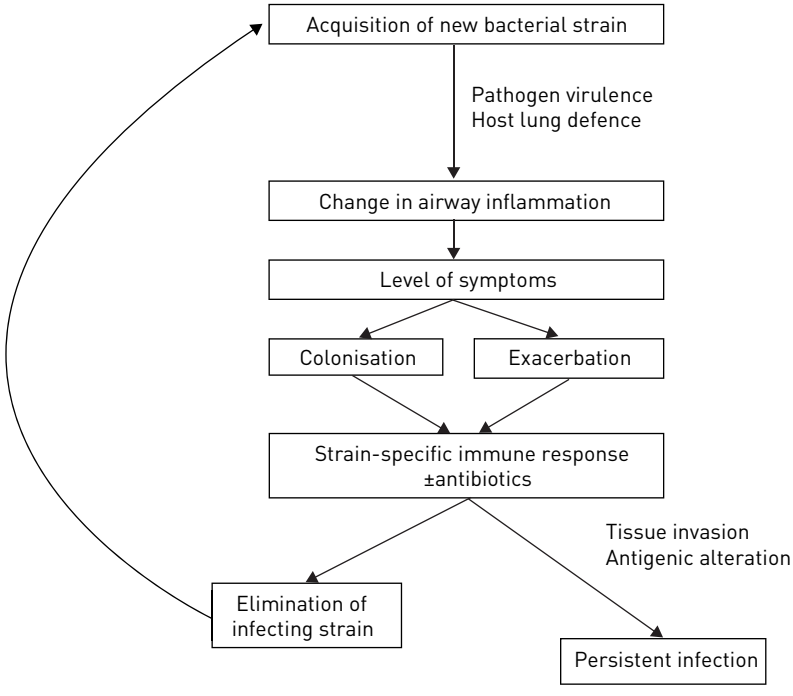

Figure 1. Current model of bacterial exacerbation pathogenesis in COPD. Reproduced and modified from [17] with permission.

 https://doi.org/10.1183/2312508X.10016216

normal lung, these inocula are dealt with quickly and efficiently with minimal inflammation by the innate defence mechanisms, such as macrophages and mucociliary clearance. However, in patients with COPD, because these defence mechanisms are compromised, and because of variation in antigenic structure among strains of these pathogens, cross-reactive acquired immunity is not effective, and these bacteria are able to persist and proliferate in the lower respiratory tract [19].

The clinical presentation of this lower respiratory tract infection by a new bacterial pathogenic strain can be an "exacerbation" or "colonisation", distinguished by whether or not the symptoms reach a level requiring the patient to seek additional treatment. A complex host–pathogen interaction in the lower airway determines this outcome, with about half of new strain acquisitions of bacterial pathogens being associated with exacerbation. The balance between host defence and pathogen virulence determines the intensity of the evoked immuno-inflammation, which in turn determines the level of symptoms. Chin *et al.* [20] demonstrated that *H. influenzae* strains associated with COPD exacerbations induced greater airway neutrophil recruitment in a mouse lung than colonisation-associated strains. Furthermore, exacerbation-associated strains interacted differently with primary human airway epithelial cells, exhibiting greater adherence and eliciting more IL-8 [21]. That the host immune response could dictate the clinical expression of a bacterial strain acquisition in COPD was suggested when immune responses to new strains of *M. catarrhalis* associated with COPD exacerbation and colonisation were compared [21]. A mucosal IgA host response (measured in sputum) to the infecting strain was more frequent and vigorous with colonisation, while a systemic IgG host response (measured in serum) was more common and intense with exacerbations [21]. A vigorous mucosal immune response could diminish bacterial interaction with airway epithelial cells, resulting in less airway inflammation and fewer clinical symptoms, thus favouring colonisation.

If the new strains were causing the exacerbation, development of an adaptive immune response would be expected and would support causation. Recent immune response studies have paid attention to possible confounding factors in older studies, and have used homologous (infecting) strains as the antigen, paired serum samples and immunoassays specific for antibodies that bind to the surface antigens of the bacterial pathogen. These studies have clearly demonstrated the development of specific antibodies following exacerbations to *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* and *P. aeruginosa*, some of which exhibit bactericidal and opsonophagocytic function, thereby aiding bacterial clearance [21–23]. However, in the case of *H. influenzae*, when the spectrum of activity of these bactericidal antibodies against a panel of strains was tested, they demonstrated a high degree of strain specificity, and only 11% of the heterologous strains were killed in these assays [22]. The strain specificity of these immune responses is because of the considerable antigenic heterogeneity of surface proteins among strains of these pathogens. As the number of strains of each of the bacteria that cause COPD exacerbations is very large, this explains how recurrent exacerbations with the same pathogenic species are seen in these patients. It also creates a challenge for vaccine development against these bacteria.

Airway inflammation during exacerbation

Although an increase in airway inflammation is seen in most exacerbations, the inflammatory process is not uniform and is related to the aetiology of the exacerbation. The distinct inflammatory profile of bacteria-associated exacerbations supports the

causative role of the isolated pathogens. As would be expected of a bacterial infection, COPD exacerbations associated with bacterial pathogens exhibit significantly more airway neutrophilic inflammation than nonbacterial episodes [24]. Furthermore, a dose–response effect is seen, whereby the intensity of neutrophilic inflammation in bacterial exacerbations is related to airway bacterial concentrations and their clinical severity [24, 25]. Several major molecular mediators of this airway neutrophilia in bacterial exacerbations have been identified, including IL-8, leukotriene B4 and TNF-α [19, 26]. Bacterial exacerbations are also associated with an IL-1β signature comprising TNF-α, granulocyte colony stimulating factor, IL-6, CD40 ligand and macrophage inflammatory protein 1 [27]. IL-17A has been associated specifically with *H. influenzae* exacerbations [28]. Neutrophil degranulation and necrosis can cause significant damage related to the release of neutrophil elastase and matrix metalloproteinases [29].

Clinical resolution of the symptoms of exacerbation is associated with a consistent decrease in mediators of neutrophilic airway inflammation, while nonresolving exacerbations demonstrate a sustained level of exaggerated airway inflammation [25]. These observations support the concept that patients can sense their airway inflammation and that resolution of this inflammation is essential for exacerbations to resolve.

Is lower airway bacterial colonisation in COPD truly innocuous?

Colonisation is defined by the absence of damaging effects to the host related to the presence of a pathogen and the absence of a specific immune response. There is now abundant evidence that neither of these two criteria is met by lower airway bacterial colonisation in COPD. Excess airway inflammation in stable COPD when colonised with bacterial pathogens has been demonstrated in several studies [29–31]. Consistent with the observations in COPD exacerbation, airway inflammation associated with bacterial colonisation is also predominantly neutrophilic, with many of the same mediators involved in bacterial exacerbations. The inflammatory profile seen with bacterial colonisation is similar to that seen with bacterial exacerbations, implying that colonisation is actually a low-grade infection.

Specific immune responses, both systemic and mucosal, to the infecting strain have now been described following colonisation, much as in exacerbations [21]. Formation of lymphoid aggregates in the small airways of patients with COPD has been described and is likely to represent a local host immune response to chronic microbial infection [32, 33]. Widespread use of HRCT scans has revealed that bronchiectasis develops in a substantial proportion of patients with COPD and is linked to chronic colonisation with potential bacterial pathogens [34].

Bacterial colonisation in COPD is associated with increased airway inflammation. It has been shown that exaggerated airway inflammation is reflected in respiratory symptoms during exacerbation. Therefore, it is likely that colonisation-induced airway inflammation in COPD is reflected in the daily symptoms experienced by these patients. Indeed, in a longitudinal study where daily symptoms were recorded and sputum samples collected every 2 weeks to assess bacterial colonisation, both airway inflammation and respiratory symptoms were significantly increased by colonisation [35]. In fact, the intensity of symptoms during bacterial colonisation was similar to that of a mild exacerbation (figure 2) [35]. This suggests that a proportion of exacerbations of COPD that are unreported are mediated by episodes of bacterial colonisation.

 https://doi.org/10.1183/2312508X.10016216

Other potential mechanisms of bacterial exacerbations

Although acquisition of new strains from the environment appears to be a major mechanism of bacterial exacerbations of COPD, it is not necessarily the only mechanism. Transition of *P. aeruginosa* from the biofilm state to a free-floating planktonic state has been associated with exacerbations of CF [36]. A similar mechanism may exist among patients with advanced COPD. A viral infection may perturb the host–pathogen balance, leading to bacterial proliferation and a prolonged exacerbation. Indeed, in a rhinoviral human experimental model of COPD exacerbation, as many as 60% of participants developed a secondary bacterial infection, which intensified the airway inflammation and lower respiratory infection symptoms [37]. Atypical bacteria play a minor role in COPD exacerbations, with *Mycoplasma pneumoniae* a rare cause and *Chlamydophila pneumoniae* implicated in 4–5% of episodes [1]. The application of microbiome techniques is also shedding new light on the mechanisms of bacterial exacerbations of COPD.

The airways microbiome changes with onset and treatment of COPD exacerbation

In approximately half of exacerbations of COPD with the clinical characteristics of a bacterial cause, bacterial pathogens are not recovered from respiratory samples by traditional culture methods [38]. This is related to the insensitivity of culture methods, as well as the focus of conventional culture techniques on the identification of known pathogens rather than on the discovery of novel ones. With their exquisite sensitivity and unsupervised nature, microbiome techniques can overcome these limitations and are beginning to be applied to understand exacerbations of COPD [3]. In a longitudinal study of bacterial infections in COPD, the sputum microbiome did not demonstrate any significant changes in community richness, evenness and diversity [39]. However, substantial taxonomic composition variation was seen during exacerbation, with an increase in *Proteobacteria* and a decrease in *Actinobacteria*, *Clostridia* and *Bacteroidia*. Furthermore, when known pathogens such as *H. influenzae* increased during an AE of COPD, closely related bacterial taxa in the phylogenetic tree were also enriched, while

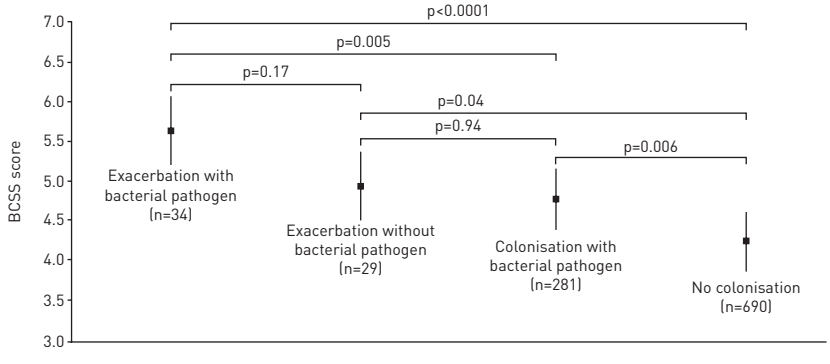

Figure 2. Breathlessness, cough and sputum scale (BCSS) score, adjusted for age and peak expiratory flow, during exacerbation and colonisation in a longitudinal study [35]. Bacterial pathogens included *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, and were detected in sputum by culture and by species-specific PCR. The BCSS score was recorded daily, while sputum samples were collected every 2 weeks. A higher BCSS score reflects a greater level of symptoms. Boxes show average BCSS score, vertical lines show standard error. Reproduced and modified from [35] with permission.

those taxa that were phylogenetically distant declined [39]. These findings suggest that, although the classical pathogens undoubtedly contribute to exacerbations, enrichment of taxa closely related to a dominant pathogen could also contribute to exacerbation pathogenesis, and that exacerbations are actually polymicrobial infections. Post-exacerbation samples showed increased bacterial abundance with only oral steroid treatment of the exacerbation, with enrichment of many taxa including *Proteobacteria*, *Bacteroidetes* and *Firmicutes*. In contrast, treatment with antibiotics only reduced bacterial abundance, specifically of *Proteobacteria*. When both steroids and antibiotics were used to treat an exacerbation, a mixed effect on the airway microbiome was seen [39].

Similar findings of microbiome dysbiosis during exacerbation were observed with an experimental human model of rhinovirus-induced exacerbations of COPD where rhinovirus was inoculated intranasally, with a decline in *Firmicutes* and *Bacteroidetes*, and an increase in *Proteobacteria*, including a 21% increase in *Haemophilus* spp. and a 9.5% increase in *Neisseriaceae* [40]. These changes were correlated with elevated neutrophil concentration and neutrophil elastase levels, and were not seen in the healthy control group [40].

Asthma

Virus-mediated exacerbations are thought to be the most common aetiology of AEs of asthma, most commonly rhinovirus, with intense airway inflammatory responses that result in symptoms of exacerbation. Bacterial causes of asthma exacerbations were first described in the paediatric literature, with a focus on atypical bacteria, such as *Chlamydia* and *Mycoplasma* spp. [41–43]. In these studies, infection was determined by convalescent serological criteria (for *Chlamydia* spp.) or IgE and skin test responsiveness (for *Mycoplasma* spp.). Specific PCR detection of *Mycoplasma* and *Chlamydia* spp. in sputum samples at asthma exacerbation was subsequently demonstrated [44–46]. Culture detection of typical bacterial pathogens in exacerbations of asthma has been examined in small studies and the yield was notably low [47]. However, similar studies have identified chronic colonisation by bacteria in children and adults with severe asthma [48, 49]. *S. pneumoniae*, *Staphylococcus aureus*, *M. catarrhalis*, *P. aeruginosa* and *H. influenzae* were the most common pathogens recovered by sputum culture during stable disease and exacerbations in these patients. This bacterial spectrum overlaps remarkably with the pathogens recovered in AEs of COPD and community-acquired pneumonia. However, the causal role of these bacterial pathogens in stable asthma and in exacerbations remains unclear.

The airway microbiota in asthma

Recent studies have increasingly used microbiome techniques to study respiratory samples in asthma to determine the prevalence and nature of dysbiosis in the flora of the lower respiratory tract. Initial microbiological characterisation of the microbiota in asthma recovered members of five major phyla: *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Fusobacteria* and *Bacteroidetes* [50, 51]. A significant increase in representation of *Proteobacteria* and a reduction in *Bacteriodetes*, *Firmicutes* and *Actinobacteria* was described compared with healthy controls [50, 51]. These changes

 https://doi.org/10.1183/2312508X.10016216

were not associated with the intensity of inhaled corticosteroid dosing and therefore could be attributable to disease [51]. Within the *Proteobacteria*, *Haemophilus* was the dominant genus detected, but *Moraxella* and *Neisseria* spp. were also detected in lower abundance [50].

Airway microbiota in severe asthma may differ based on asthma phenotype and whether the airway inflammation is IgE-mediated or neutrophil-mediated, but differences in sampling technique among studies make definitive conclusions difficult [52]. Severe resistant neutrophilic asthma was associated with an increased abundance of *Proteobacteria*, with *Haemophilus*, *Moraxella* and *Streptococcus* spp. dominant in induced sputum [53]. Increased abundance of any of these three pathogens correlated with airway neutrophil counts, increased IL-8 and more severe airflow obstruction. Individually, increased abundance of *Moraxella* spp. had the strongest correlation [53]. Bronchial biopsies from the BOBCAT (Bronchoscopic exploratory research study of biomarkers in corticosteroid-refractory asthma) study demonstrated a significant correlation with increased abundance of *Proteobacteria* and worsening asthma control scores [48]. Specifically, a greater abundance of *Enterobacteriaceae*, *Neisseriaceae* and *Pasteurellaceae* was seen, with the largest difference observed for a *Klebsiella* sp. [54]. Improving asthma control scores were associated with a greater abundance of *Actinobacteria*, which was also associated with a response to steroids [54]. In severe IgE-mediated asthma, there were differences in the airway microbiota from mucosal biopsy specimens and airway lining fluid aspirates, although the pattern of a greater relative abundance of *Bacteriodetes* and *Firmicutes* relative to *Proteobacteria* was common to both samples [52]. The dominant genera in the bronchial biopsies were *Streptococcus* and *Prevotella*. Members of the genera *Legionella* and *Haemophilus* were found in all bronchial biopsies with >2% relative abundance, the first study to report a significant presence of *Legionella* spp. [52]. Greater diversity of the airway bacterial community has been positively associated with more bronchial hyperresponsiveness and with being more likely to show a reduction in this hyperresponsiveness in response to clarithromycin [55].

Role of antibiotics in asthma

Although it is likely that airway dysbiosis plays a role in asthma exacerbations, there is as yet no reliable data on changes to the airway microbiome implicated in AEs of this disease. Although antibiotics are used in asthma exacerbations, placebo-controlled antibiotic trials during AEs have been limited to the macrolide class of antimicrobials, and have not shown consistent benefit in reducing symptom scores or improving QoL [56]. Telithromycin, a semi-synthetic macrolide derivative, demonstrated a small improvement in symptoms in less severe AEs (determined by only one-third of enrolled patients receiving concomitant oral or parenteral corticosteroids), but had no effect on lung function [57]. Toxicity concerns and a lack of confirmation of these findings have limited the use of telithromycin in exacerbations of asthma.

Similarly, despite the emerging evidence of macrolide-responsive potentially pathogenic bacteria dominating the airway microbiota in asthma, clinical trials of long-term macrolide therapy in chronic asthma have had conflicting results, without clear evidence of improvement [58]. Subgroup analyses suggested a potential benefit in noneosinophilic asthma, but additional trials in this subgroup are required [58]. A reduction in the relative abundance of many genera members after treatment, including *Prevotella*, *Staphylococcus*,

Pseudomonas and *Haemophilus* spp., and a reduction in diversity as noted by the mean number of genera detected was seen in a paired analysis of the airway microbiota in asthma before and after macrolide treatment [59].

Non-CF bronchiectasis

Infection is often the initial insult in the development of NCFB, following a severe bacterial pneumonia [60]. Pertussis, tuberculosis, mycoplasma infection and viral pneumonias (influenza virus, respiratory syncytial virus and adenovirus) have also been implicated in the development of NCFB [61, 62]. Bacterial infection is thought to be a major driver of the progression in NCFB by a "vicious circle" of infection and inflammation [63]. In established disease, bacteria are often detected by culture in stable disease, and have been presumed to be the aetiological agent of a subsequent exacerbation due to increased bacterial load. Whether increased bacterial load is the actual underlying mechanism of NCFB exacerbation or whether alternative pathways such as a change in bacterial strain or alterations in microbial biofilms are responsible has not been studied systematically. The most commonly recovered bacteria are *H. influenzae* in both adults and children with NCFB, followed by *S. pneumoniae*, *M. catarrhalis* and *P. aeruginosa*. Adults with NCFB are more likely to have *P. aeruginosa* recovered by culture than children [64]. All of the early studies used culture detection methods, although microbiome studies have now been published.

The airway microbiota in NCFB in stable disease and exacerbation

Recent work by Tunney *et al.* [65] has allowed direct comparison of microbiome assessment by culture detection during both stable disease and during exacerbation in NCFB. Culture-detected sputum bacterial colonisation in stable disease was consistent with previously published data, and included *H. influenzae*, *P. aeruginosa* and *S. aureus*, in decreasing order of frequency of detection. Anaerobic bacteria were also detected in culture at high frequency, with *Prevotella* and *Veillonella* spp. most commonly recovered. The same pathogens were recovered by culture during exacerbation before antimicrobial therapy, with little change in the frequency of detection after antimicrobial treatment. The airway microbiota from stable disease demonstrated members of four dominant phyla, with *Proteobacteria* having the greatest abundance, followed by *Firmicutes*, *Bacteroidetes* and *Fusobacteria*. Within these phyla, the most abundant genera were *Haemophilus*, *Streptococcus*, *Pseudomonas* and *Achromobacter*. There was no significant change in the microbial community structure with disease exacerbation, although there was greater microbial diversity observed with clinically stable disease. However, there was no correlation between microbial diversity and lung function, unlike the situation in CF [65].

A longitudinal assessment of changes in the airway microbiome in NCFB confirmed *H. influenzae* as the most abundant microorganism in stable disease, followed by *P. aeruginosa* and *Streptococcus* spp., with no significant changes over the 6-month study period [66]. The finding of mucoid *P. aeruginosa* was associated with a reduction in alpha diversity that was independent of the severity of lung function. When compared with sputum samples during exacerbation, treatment or recovery, there was no significant difference in bacterial load or diversity [66]. This finding calls into question the long-standing premise of increased bacterial growth of a previously colonising pathogen as responsible for the exacerbations in NCFB.

 https://doi.org/10.1183/2312508X.10016216

Role of antibiotics in NCFB

There have been no RCTs evaluating the effectiveness of antibiotics in acute NCFB exacerbations, but there is a substantial amount of nonrandomised evidence to support improvements in symptoms and faster resolution with their use. Macrolides (azithromycin and erythromycin) administered chronically over 6–12 months have been shown recently to reduce exacerbation frequency and to improve or slow the rate of lung function decline [67–69]. In the BLESS (Bronchiectasis and low-dose erythromycin study) trial, subgroup analysis suggested that the greatest reduction in exacerbations occurred in patients who had *P. aeruginosa* present at the trial inception [67]. This distinction in response rate by the presence of baseline *P. aeruginosa* was not observed for azithromycin [68]. There was a significant increase in the rate of macrolide resistance (up to 88% of pathogens, and up to a 40% increase in pneumococcal macrolide resistance) with chronic use.

Using samples obtained in the BLESS trial, Rogers *et al.* [70] examined baseline and post-treatment airway microbiota profiles to determine whether clinical benefits were related to changes in the airway microbiota. Patients whose microbiota was not dominated by *P. aeruginosa* at baseline had a significantly greater within-patient change in microbiota composition in the erythromycin-treated group compared with placebo, with a significant reduction in the relative abundance of *H. influenzae* and an increase in that of *P. aeruginosa*. There were no significant microbiota changes over time in response to erythromycin if *P. aeruginosa* dominated at baseline.

The findings of these studies support the judicious use of antimicrobial treatment of exacerbations of NCFB, and at least short-term (1-year) use of macrolides to reduce exacerbation frequency in patients with more than three exacerbations annually. The effect and mechanism of exacerbations and antimicrobial treatment in NCFB remain poorly defined and require further investigation. The increase in *P. aeruginosa* after 48 weeks of treatment with erythromycin should also give pause for thought, as a *P. aeruginosa*-dominated airway microbiota has been associated with more severe and progressive disease [71].

Cystic fibrosis

CF is a disease where the majority of severe morbidity is driven by lung disease with airway obstruction and chronic bacterial infection. CF airway infections are frequently polymicrobial [72]. This has prompted multipronged research studies with the aim of understanding the role of bacterial infection in CF airways at baseline and during exacerbation.

Are bacteria responsible for CF exacerbations?

Because of the universal substantial bacterial colonisation seen in CF, traditional culture techniques are of little help beyond enumerating the major pathogens in helping us understand the role of bacteria in CF exacerbations. Acquisition of new strains was examined for *P. aeruginosa* in a small study and was not found to be related to exacerbations, as it is for COPD [73]. Whether strain changes are relevant to exacerbations associated with other pathogens in CF has not been examined systematically.

With the advent of microbiome techniques, there has been renewed interest in examining the bacterial pathogenesis of CF exacerbations; however, the results of the many studies

performed to date have been variable. Fodor *et al.* [74] examined the microbiome of 23 adult CF patients in expectorated sputum and oral wash samples obtained during an AE, after antibiotic treatment and during stable disease, and found a similar microbe composition in the three sample collection time periods. They concluded that exacerbations in CF were not related to acute changes in the airways microbiome. Conversely, Carmody *et al.* [75] explored the microbiome of 68 paired sputum samples at baseline and during exacerbation from 28 CF patients, and found that the abundance of members of the genus *Gemella* was increased during exacerbation compared with baseline samples. Similarly, Twomey *et al.* [76] analysed sputum from CF patients with and without exacerbation, and found an alteration in the anaerobic bacterial population, namely in members of the order *Chrysiogenales*. A longitudinal metagenomics analysis of CF sputum samples from three patients before, after and during exacerbation demonstrated a diverse microbiota composition with changes over time [77].

There are few data on the immunological mechanisms that support bacterial involvement in CF pulmonary exacerbation. Inflammation is a key driving factor in the pathogenesis of airway disease progression in CF. There are novel and consistent findings across studies that have related the inflammatory response during a CF pulmonary exacerbation to airway microbiology that support bacterial causation. However, a key finding is that airway microbial diversity and the relative abundance of different bacteria may be more important than the presence or absence of any one particular organism in causing exacerbations of CF. Obligate and facultative anaerobes play a role in airway microbial balance, with alterations in this balance corresponding to increased airway inflammation and decreased lung function during CF exacerbation. Zemanick *et al.* [78] performed a study to examine the relationship between airway microbiota and specific genera, biomarkers of airway and systemic inflammation, and lung function in individuals with CF at the beginning of a pulmonary exacerbation and how these factors changed after antibiotic therapy. *Staphylococcus* and *Pseudomonas* spp. were positively correlated with sputum neutrophils and circulating CRP, while *Veillonella*, *Granulicatella* and *Prevotella* spp. were negatively correlated. Higher concentrations of inflammatory markers in sputum and a higher relative abundance of *Pseudomonas* spp. were associated with worse lung function. Interestingly, total bacterial load and specific bacteria measured at early treatment by quantitative PCR were generally not as strongly correlated with lung function and inflammatory markers as the lower diversity and relative abundance of one organism: a change in the relative abundance of *Pseudomonas* spp. with treatment was associated with improvement in lung function and decreased markers of inflammation [78]. This correlation suggests that alterations in the microbiome play a role in CF exacerbations.

In another study by Sagel *et al.* [79], several systemic measures of inflammation changed with antibiotic therapy of exacerbations and reliably distinguished exacerbations from stable disease. At the onset of exacerbation, plasma CRP, serum amyloid A, calprotectin and neutrophil elastase–antiprotease complexes were most strongly correlated with clinical measures of disease. At the end of exacerbation, therapy with antibiotics and reductions in CRP, serum amyloid A, IL-1 receptor antagonist and haptoglobin showed the best clinical association [79]. These measures of systemic inflammation generally reflect bacterial infection and their course during an exacerbation, and with antibiotic therapy support a bacterial cause of exacerbations.

To the best of our knowledge, there have been no placebo-controlled antibiotic trials in CF exacerbation; however, trials of antibiotic prophylaxis provide valuable insights into the bacterial ecology in CF. When inhaled tobramycin was administered for three cycles of

 https://doi.org/10.1183/2312508X.10016216

28 days followed by an interval of 28 days, in spite of the waning of its effect on sputum density of *Pseudomonas* over successive cycles, clinical benefits of reduced exacerbations and improvements in pulmonary function were maintained [80]. This suggests that the effects of antibiotics in addition to known bactericidal activity, such as anti-inflammatory effects or alteration of bacterial virulence, are important in CF. Similar studies performed recently predominantly with inhaled aztreonam have demonstrated microbiome alterations with inhaled antibiotics [81, 82], again showing that it is the balance rather than the quantity of bacteria that is important in CF.

Predominant bacteria and antimicrobial resistance

The bacteria found in the airways of patients with CF vary over time, and different bacteria are typically acquired with age (figure 3). *S. aureus* and nontypeable *H. influenzae* are often the earliest organisms to become chronic colonisers [84]. *P. aeruginosa*, MRSA, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Alcaligenes* spp., *Aspergillus* spp. and NTM are found variably in individuals as they age. Given the diverse microbiome of the lungs, a strongly implicated pathogenicity of a given bacteria in any given exacerbation is not routinely feasible. For most organisms except for *P. aeruginosa*, MRSA and *B. cepacia* complex, there is still debate about their importance in the pathogenesis of CF lung infection [85, 86]. *P. aeruginosa* is clearly the most common and significant pathogen in CF. Approximately 80% of individuals with CF are eventually infected with *P. aeruginosa*, and acquisition of *P. aeruginosa*, particularly organisms producing mucoid exopolysaccharide, is associated with clinical deterioration [87, 88]. *B. cepacia* complex is classically feared due to the association with a rapid decline in lung function upon acquisition; however, there are significant variations in virulence among the different genomovars of *B. cepacia*.

Initial isolates of *P. aeruginosa* from patients with CF are commonly susceptible to antipseudomonal β-lactam antibiotics, aminoglycosides and fluoroquinolones. Over time, however, antibiotic resistance develops. Multiple antibiotic resistance, defined as *in vitro* susceptibility to only a single class of antimicrobial agents, has been reported in 11–17% of

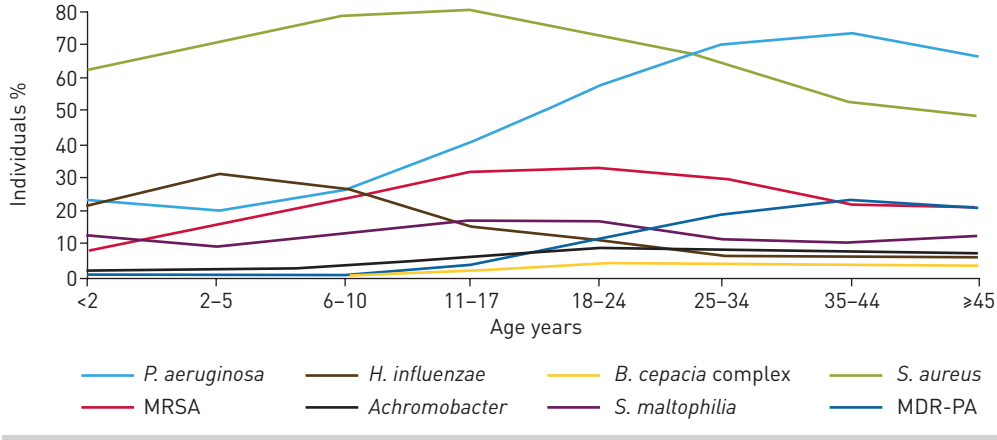

Figure 3. Changes in the prevalence of bacterial pathogens with age in CF. The bacterial pathogens examined were *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Burkholderia cepacia* complex, *Staphylococcus aureus*, MRSA, *Achromobacter*, *Stenotrophomonas maltophilia* and multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA). Reproduced and modified from [83] with permission.

P. aeruginosa isolates from individuals with CF around the world [89]. Despite this daunting statistic, standard susceptibility testing has not been clearly shown to improve patient outcome [90, 91]. Recent data from the Cystic Fibrosis Foundation in the USA found that 26% of *S. aureus* was methicillin resistant. *B. cepacia* complex organisms are often resistant to multiple antibiotics. They are intrinsically resistant to the aminoglycosides and usually resistant to β-lactam antibiotics with the exception of meropenem, but often are initially susceptible to the fluoroquinolones, although resistance develops rapidly [92]. *S. maltophilia* and *A. xylosoxidans* also pose antibiotic resistance challenges [93, 94].

Idiopathic pulmonary fibrosis

The traditional view is that IPF is a noninfectious parenchymal lung disease. Exacerbations of IPF are often treated with antibiotics, but evidence of infection, whether bacterial or viral, is usually not detected by traditional culture techniques. Microbiome techniques have recently been applied to characterise the lower airway microbiota in IPF with interesting and provocative findings. In stable IPF, specific operational taxonomic units of *Streptococcus* and *Staphylococcus* spp. have been associated with disease progression [95]. In another study, the bacterial burden in IPF bronchoalveolar lavage samples was greater than in healthy controls and in COPD subjects, and *Haemophilus*, *Neisseria*, *Streptococcus* and *Veillonella* spp. were overrepresented [96]. These findings come with the caveat that, in both of these studies, measures to prevent upper airway contamination of lavage samples were not taken, as evidenced by the substantial bacterial burden in the healthy controls [96]. Only one pilot study has attempted to study the bronchial microbiome in patients with IPF during exacerbation and compare it with stable disease [97]. A greater bacterial abundance was seen in exacerbation samples, with a trend for increased *Proteobacteria*.

The role of the microbiome in IPF warrants further investigation. Bronchiectasis is common in advanced IPF and has been attributed to traction from parenchymal fibrosis. It is possible that a vicious circle of infection and inflammation could develop because of impaired bacterial clearance in these distorted airways, much as has been described for COPD, and could contribute to progression and exacerbations [3].

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Disclosures: None declared.

Chapter 9

Differential diagnosis and impact of cardiovascular comorbidities and pulmonary embolism during COPD exacerbations

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The inflammatory responses and triggers of COPD exacerbations are heterogeneous, and these events are increasingly recognised as episodes with enhanced risks. As exacerbation diagnosis is based on symptoms rather than objective measures, other pathologies may mimic its presentation. Myocardial infarction and heart failure are common in exacerbating patients, and those with elevated cardiac biomarkers have increased odds for mortality. In additional to traditional risk factors, other or enhanced risk factors may contribute to the observed increase in cardiovascular risk during exacerbations. Furthermore, a high prevalence of pulmonary embolism has been observed in COPD patients with exacerbation, mainly in those with absence of lower respiratory tract infection symptoms or other obvious aetiologies. Healthcare professionals caring for COPD patients with exacerbations should be aware of the differential diagnosis of these events and consider additional diagnostics following clinical suspicion. The current literature suggests that diagnostic algorithms and pharmacological treatment of non-COPD-related events during COPD exacerbations are comparable to stable-state and other patient groups.

Cite as: Franssen FME, Vanfleteren LEGW. Differential diagnosis and impact of cardiovascular comorbidities and pulmonary embolism during COPD exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 114–128 [https://doi.org/10.1183/2312508X.10016316].

Exacerbations are considered pivotal events in the progression of airflow limitation in COPD [1] and are associated with poor health status [2]. Moreover, hospitalisations for exacerbations account for a large proportion of the economic burden of COPD worldwide [3] and are related to poor survival; it was shown that 50% of patients hospitalised for an exacerbation for the first time died within 3.6 years [4].

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Respiratory viral infections, airway bacteria and environmental factors are the most frequent triggers of exacerbations in susceptible hosts [5]. They result in increased airway inflammation, causing airway oedema, bronchoconstriction and increased sputum production [6]. While exacerbations are typically associated with increased neutrophilic airway inflammation [7], the inflammatory response during these events is largely heterogeneous. Based on sputum and serum biomarkers, four distinct biological exacerbation clusters have been identified, termed "bacteria predominant", "eosinophil predominant", "virus predominant" and "pauci-inflammatory" [8]. This last exacerbation phenotype was found to represent 11% of the total number of events and was characterised by limited changes in the inflammatory profile and fewer events associated with known aetiology [8]. Remarkably, patients in this cluster had the lowest FEV1, the most pronounced decline in FEV1 following exacerbation, the highest exacerbation rate in the previous year and the highest number of pack-years [8]. Although these differences were too small to be distinguished clinically, they emphasise the clinical relevance of this group and the need to study the pathophysiological mechanisms underlying these pauci-inflammatory exacerbations. In fact, while defined by a flare-up of respiratory symptoms in patients with underlying COPD, it is likely that the term "exacerbation" is a misnomer for at least some of these pauci-inflammatory events. Other acute diseases or acute worsening of chronic co-occurring conditions may be the cause of the increased symptomatology in these COPD patients.

Comorbidities are defined as the presence of one or more additional diseases co-occurring with COPD, and have a negative impact on morbidity and mortality in this disease [9, 10]. While some comorbidities may develop independently of COPD, others may be causally related either by shared risk factors (*e.g.* smoking, reduced physical activity) or by syndemic interactions in which there are deleterious biological or behavioural interfaces that enhance the negative health effects of COPD and other diseases that may be present [11]. Comorbidities are common at any stage of airflow limitation [12], and commonly remain undiagnosed and untreated [13]. For example, subclinical right ventricular dysfunction and remodelling were observed in COPD patients without pulmonary hypertension [14]. Indeed, due to an overlap in symptoms (*e.g.* dyspnoea and wheeze) and clinical signs, the differential diagnosis of COPD and comorbidities can be difficult in the stable state as well as during exacerbation, and includes cardiovascular disease and pulmonary embolism.

Cardiovascular comorbidities

Comorbid chronic cardiac disorders are common in patients with COPD. Although there is a wide variation in estimates of their epidemiology, the prevalence and incidence of cardiac comorbidities are higher in patients with COPD than in age- and sex-matched non-COPD subjects, after also taking into account the previous history of cardiovascular events, diabetes, hypertension and hypercholesterolaemia [15]. In addition, the ECLIPSE (Evaluation of COPD longitudinally to identify predictive surrogate end-points) study reported that cardiovascular comorbidities, including myocardial infarction, chronic heart failure and arrhythmia, are more frequently present in patients with stable COPD than in control smokers and nonsmokers after adjustment for age and sex [16]. This suggests that additional risk factors for cardiovascular disease are present in subjects with chronic airflow limitation that contribute to this disproportionate prevalence. Low-grade systemic inflammation, oxidative stress, arterial stiffness, abdominal obesity [17] and hypoxaemia have been linked to cardiovascular risk in COPD [18]. Irrespective of its risk factors, when

coexisting with stable COPD, cardiovascular disease has increased odds of mortality, and is associated with increased respiratory symptoms and with reduced health status and functional exercise capacity [16, 19].

The differential diagnosis of cardiovascular disease in patients with stable COPD can be challenging, especially in older and smoking subjects complaining of nonspecific symptoms, such as dyspnoea, fatigue, chest tightness and reduced exercise tolerance. Thus, underdiagnosis is common. In a population of stable patients with COPD managed in a primary care setting, 21% of patients had previously unrecognised heart failure [20]. In addition, in COPD patients referred for pulmonary rehabilitation, 14% of patients with ischaemic ECG changes had no previous history of cardiovascular disease [21], and echocardiographic abnormalities occurred in almost 54%, of which two-thirds were previously unknown [22]. Adequate diagnosis and treatment of cardiovascular disease in COPD is expected to reduce the burden of disease and increase survival, as cardiovascular disease is the major cause of death in mild to moderate disease [23].

In accordance with these observations in COPD populations, chronic airflow limitation is common in patients with acute and chronic cardiovascular disease. A multicentre European study including a large population of patients with stable ischaemic heart disease (IHD) reported post-bronchodilator airflow limitation in 31% of subjects, and the majority of these had no previous spirometry testing or diagnosis [24]. In patients with IHD undergoing percutaneous coronary intervention, 25% met the spirometric criteria for COPD, and these had an independently increased mortality risk and a higher number of cardiovascular events during follow-up [25]. Thus, there is a rationale for screening cardiovascular patients for the presence of undiagnosed COPD in both acute and chronic settings [26].

Exacerbations and cardiovascular comorbidities

Although major (dyspnoea, sputum purulence, sputum volume) and minor (rhinitis, wheeze, cough and sore throat) symptomatic criteria for exacerbations are available [19], misdiagnosis of episodes of cardiovascular disease during these events may occur. Symptoms such as dyspnoea and chest pain may be interpreted as exacerbation related, even when their origin is cardiac disease. Exacerbations may also be accompanied by acute cardiovascular events. In fact, exacerbations are increasingly recognised as episodes with elevated cardiovascular risk, and the presence of cardiovascular disease predicts short- and long-term mortality after exacerbation [27, 28], irrespective of the degree of airflow limitation [29]. In addition, in COPD patients with cardiovascular disease, symptom recovery time after exacerbation is longer [19], while exacerbation frequency *per se* is not increased [5]. The number of cardiovascular comorbidities also does not seem to affect the susceptibility to exacerbations [19]. Although numerous studies have addressed the incidence, prevalence and impact of cardiovascular disease during exacerbations in recent decades, results vary substantially with the diagnostic criteria applied, the severity of exacerbations included and the type of cardiovascular disease studied.

Occult myocardial dysfunction is common in exacerbations. Brekke *et al.* [30] performed a retrospective analysis of ECGs recorded on hospital admission and found that 28% of hospitalised elderly COPD patients had an increased cardiac infarction injury score on the ECG from the day of admission for an AE, of whom only 30% had a previous history of

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myocardial infarction. Female patients and younger age groups were more likely to be undiagnosed. Cardiac infarction injury score was an independent predictor of mortality risk during follow-up in these patients [30]. No additional assessments were performed to establish the diagnosis of IHD, however, which is an important limitation of the study. Using anonymised medical records in a UK administrative database, Donaldson *et al.* [31] reported a 2.27-fold increased risk of myocardial infarction in the 5 days after the start of pharmacological treatment for an exacerbation. Patients with more frequent exacerbations had higher incident rates of myocardial infarction. The risk of stroke was also increased 1.26-fold in the 7 weeks after an exacerbation.

Cardiac troponin is a biomarker of cardiac injury, used for the evaluation of patients with suspected acute coronary syndrome, although raised levels can be caused by other aetiologies of acute injury, such as pulmonary embolism. Raised troponin is very common in patients admitted to hospital with exacerbation of COPD, and also in the absence of signs and symptoms of comorbid myocardial ischaemia or pulmonary embolism, and is associated with increased risk of all-cause mortality [32]. While increased troponin could indeed be a marker of more severe COPD, the association is partly explained by the degree of tachycardia [33], and in some patients it may represent silent myocardial ischaemia. In a prospective cohort study of exacerbated and hospitalised patients, 10% of patients had elevated serum troponin and 8.3% had a combination of raised troponin and acute ischaemic ECG changes and/or chest pain [34], thus meeting the diagnostic criteria for myocardial infarction. Pizarro *et al.* [35] reported that two-thirds of COPD patients with increased plasma troponin presenting at the emergency department with an exacerbation had IHD, assessed using invasive coronary angiography. Almost 40% of the total study population required revascularisation. Neither the prevalence of IHD nor the need for intervention differed among COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages [35].

Left ventricular dysfunction in COPD patients may be associated with exacerbation without being the cause of this event. In a population of COPD patients admitted to an ICU, 31% of exacerbations were clinically associated with acute left-heart dysfunction, while in another 14%, left ventricular dysfunction was possibly present [36]. In another study of patients with severe exacerbation admitted to the ICU because of the need for mechanical ventilation, previously undiagnosed left ventricular dysfunction was revealed in 41% [37]. Rather unexpectedly, these patients recovered faster and had a better prognosis than those with normal heart function, which was attributed to the maximal medical treatment of these patients.

In addition to heart failure with a reduced left ventricular ejection fraction, approximately half of patients have heart failure with a preserved left ventricular ejection fraction (HFpEF) and an abnormal left ventricular diastolic function [38]. Diagnosing HFpEF in the context of COPD is difficult, due to challenges in the noninvasive echocardiographic assessment of hyperinflated patients in acute respiratory distress, the increased levels of biomarkers associated with COPD and the presence of other comorbidities. Marcun *et al.* [39] studied the prevalence of HFpEF in COPD patients hospitalised for exacerbation using international criteria for this condition. After exclusion of patients with a reduced ejection fraction, 19% met the criteria for HFpEF. These patients were older, more frequently had hypertension and atrial fibrillation, more often used cardiac medications and had increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) than those without this condition. While the degree of airflow limitation and diffusion capacity were comparable

between patients with and without HFpEF, COPD GOLD stage and elevated NT-proBNP but not the presence of HFpEF were independent predictors of long-term mortality [39]. In addition, in patients with physician-diagnosed COPD exacerbation, but without clinical evidence of acute cardiac disease, admitted to a public hospital, elevated NT-proBNP on admission was identified as a strong predictor of early mortality independently of other known prognostic indicators [40]. Hence, NT-proBNP might be a useful biomarker in COPD to stratify increased cardiovascular risk during exacerbations.

Atrial fibrillation is characterised by disorganised atrial activation and ineffective atrial contraction, with irregular conduction to the ventricle. It is the most common arrhythmia in patients with stable COPD [41], and is associated with morbidity and mortality. Increased dyspnoea is an important symptom of atrial fibrillation, and thus this condition may be misdiagnosed as COPD exacerbation. Since both conditions share several risk factors, including smoking, cardiac diseases and hypoxaemia, it can be anticipated that atrial fibrillation is even more prevalent during exacerbations of COPD. In addition, an increase in pulmonary hypertension during exacerbation may result in right atrial pressure overload, with consequent volume stretch and arrhythmia. Indeed, in a study with patients consecutively hospitalised for COPD exacerbation and hypercapnic respiratory failure, Terzano *et al.* [42] reported that 21.7% had an episode of paroxysmal atrial fibrillation. Patients with atrial fibrillation were older, more frequently males, had reduced FEV1 and elevated $PaCO_2$, and had increased pulmonary artery systolic pressures, compared with those without atrial fibrillation [42].

Additional cardiovascular risk factors during exacerbations

The mechanisms underlying the increased cardiovascular risk in COPD patients with stable disease appear to be intensified during exacerbation, and additional risk factors may come into play (figure 1).

It has long been considered that low-grade systemic inflammation is a hallmark of patients with COPD [43]. Recent studies, however, have indicated that persistent systemic inflammation is present in a minority of COPD patients only [44]. Compared with the inflammatory response in smokers without chronic airflow limitation, increased plasma levels of fibrinogen, IL-6, CRP and white blood cells were reported in stable COPD patients [44]. Remarkably, patients with COPD with persistent systemic inflammation had more frequent exacerbations and a higher prevalence of cardiovascular disease compared with patients without systemic inflammation, despite comparable age and sex. Previously, Wedzicha *et al.* [45] also observed increased plasma levels of fibrinogen and IL-6 in the stable state in exacerbating patients. Moreover, they reported increases in these inflammatory markers during AEs, and hypothesised that this may contribute to the acutely increased cardiovascular risk during these events [45]. It is currently hypothesised that these acute elevations in inflammatory mediators during exacerbations are caused by respiratory tract infections, which frequently trigger these events. Indeed, it is known that acute respiratory tract infections are associated with an increased risk of acute myocardial infarction for a period of about 2 weeks [46].

Exacerbations result in worsening of airflow obstruction and lung hyperinflation [47]. Since hyperinflated patients have impaired left ventricular diastolic filling patterns and decreased cardiac chamber sizes, it has been postulated that dynamic hyperinflation during exacerbation might contribute to the development of heart failure [48].

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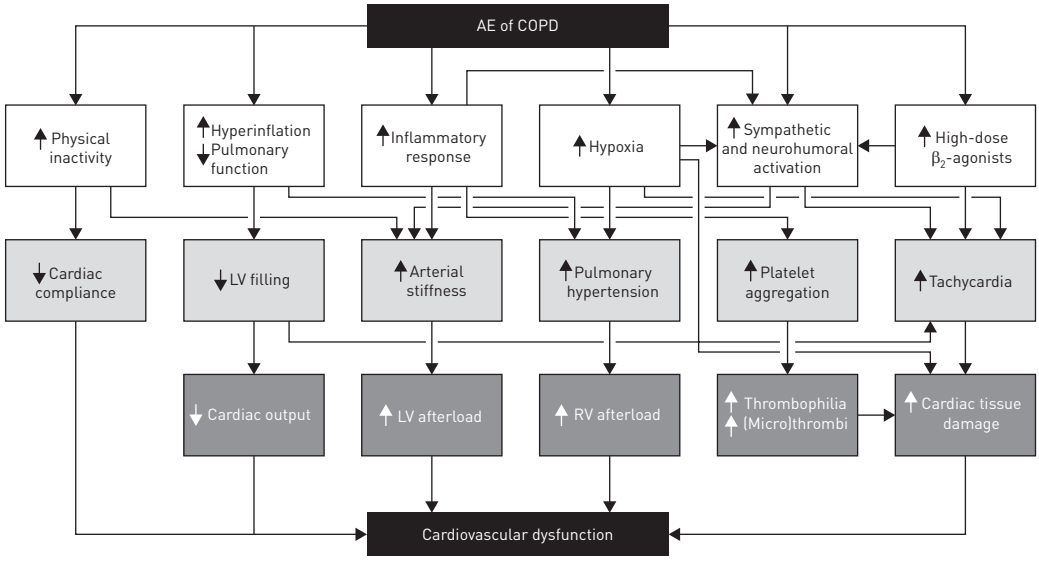

Figure 1. Potential mechanisms underlying the increased cardiovascular risk during COPD exacerbations. COPD exacerbations may be associated with physical inactivity, impaired pulmonary function, an increase in hyperinflation, an inflammatory response in the lungs and circulation, hypoxia and sympathetic activation. Exacerbations are commonly treated with high-dose β_2-agonists. These factors may all contribute to different extents to changes in cardiac pre- and afterload by changes in left ventricular (LV) filling, pulmonary hypertension and arterial stiffness, an increase in tachycardia and increased platelet aggregation. This may result in reduced cardiac output, increased cardiac afterload and increased thrombophilia leading to (micro)thrombi, potentially leading to cardiac damage and direct cardiac tissue damage from hypoxia. Tachycardia may also contribute to cardiovascular dysfunction in exacerbation. RV: right ventricular.

Acute respiratory failure may occur during exacerbations; it is an important reason for hospitalisation, and may contribute to the increased cardiovascular risk during these events. Hypoxaemic COPD patients can be characterised by a reduced platelet aggregate ratio in comparison with nonhypoxaemic patients, suggesting that these patients have more active platelets with increased tendency to aggregate in the circulation [49]. In addition, thrombocytosis is commonly observed during exacerbations and has been associated with hypercapnic respiratory failure and long-term oxygen therapy use [50]. It was also an independent predictor of short-term and 1-year mortality after exacerbation [50].

Intensification of treatment with short-acting inhaled β_2-agonists, with or without short-acting anticholinergics, is recommended as the initial treatment for a COPD exacerbation [51]. It is well recognised that β_2-agonists result in increased heart rate and reduced potassium concentrations. Treatment with β_2-agonists also significantly increases the risk for a cardiovascular event compared with placebo [52].

Arterial stiffness, a validated noninvasive biomarker of cardiovascular risk, is increased in patients with stable COPD compared with sex-, age- and smoking-matched controls, and is related to exacerbation frequency [53]. Patel *et al.* [54] observed acute elevations in arterial stiffness and cardiac biomarkers at exacerbation compared with the stable state. This rise in arterial stiffness was most pronounced in those with airway infection, and was independent of other factors possible contributing to cardiovascular risk during exacerbation, such as changes in heart rate, blood pressure and oxygen saturation. This suggests that increased arterial stiffness is an additional risk factor for cardiovascular disease during exacerbation,

although others observed no difference in arterial stiffness between COPD patients with and without a need for coronary revascularisation during an episode of exacerbation [35].

Physical activity is reduced early in the course of COPD, and is most pronounced in patients with symptoms of dyspnoea and lower levels of exercise capacity [55]. Moreover, inactivity is even more pronounced during hospitalisation for an exacerbation and in those with a hospitalisation in the previous year [56]. Since physical inactivity is associated with increased risk of cardiovascular disease, this factor may contribute in exacerbated COPD patients. Indeed, bed rest was found to induce a significant increase in carotid and superficial femoral artery wall thickness in male subjects [57].

While the relative contribution of each of these risk factors is unknown, the effects of systemic inflammation, dynamic hyperinflation, hypoxaemia, increased β_2-agonist use, arterial stiffness and physical inactivity may be synergetic during exacerbation (figure 1).

Clinical implications of cardiovascular comorbidities

There is almost no evidence to guide the management of cardiovascular disease in the setting of COPD exacerbation. Simple and inexpensive biomarkers, such as troponin and NT-proBNP, may help identify exacerbating patients with increased risk of cardiovascular events and mortality. Studies are needed to develop diagnostic algorithms and interventions to prevent and treat cardiovascular comorbidities in the setting of an AE. Based on discussions of specific risk factors for cardiovascular disease during exacerbation, the effects of anti-aggregate, anti-inflammatory and lung volume-reducing strategies, as well as oxygen therapy and physical activity promotion, on the risk of cardiovascular complications during exacerbations and on long-term outcomes warrant further investigation.

Antiplatelets

With evidence for thrombocytosis and the pro-inflammatory properties of platelets, antiplatelet therapies have been proposed in COPD. In an observational cohort study of patients hospitalised with AE, aspirin or clopidogrel treatment correlated with a reduction in 1-year mortality but not in in-hospital mortality [50]. A systematic review and meta-analysis including three studies with patients with an exacerbation at the time of enrolment and two studies with patients with stable disease showed a 19% reduction in all-cause mortality in those patients receiving antiplatelet treatment compared with those not receiving antiplatelets [58]. While prospective evidence advocating the use of antiplatelet therapies in COPD is lacking, several studies have investigated the biological and clinical differences between different platelet inhibitors. In patients with stable IHD and concomitant COPD undergoing percutaneous coronary intervention, ticagrelor, a newer P2Y12 inhibitor, was superior in improving surrogate markers of endothelial function and resulted in higher platelet inhibition compared with clopidogrel [59]. In patients with acute coronary syndrome and comorbid COPD, ticagrelor *versus* clopidogrel reduced and substantially decreased the absolute risk of ischaemic events (by 5.8%), although it was more commonly associated with dyspnoea [60].

Statins

For a long time, the anti-inflammatory effects of statins have been discussed as a possible treatment to prevent COPD exacerbations and reduce the cardiovascular complications of these events. Retrospective studies reported that treatment with statins was associated with

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improved survival after COPD exacerbation [61]. However, an RCT investigating the effects of simvastatin *versus* placebo on exacerbation rates in COPD patients without cardiovascular risk or indication for statins did not show any benefits of this intervention [62]. Hence, there currently is no respiratory indication to prescribe statins in COPD.

β-blockers

Multiple observational studies have shown that the use of cardioselective β-blockers is associated with a reduction in overall mortality and exacerbation frequency, and with better outcomes during and after hospitalisation for acute COPD exacerbation [63–65]. Beneficial effects of β-blockers on exacerbations in all patients, including those on oxygen therapy, were also reported in the observational COPDGene cohort [66]. A prospective RCT has not yet been published, but is currently underway in the USA (ClinicalTrials.gov, trial number NCT02587351). The (potential) pathophysiological mechanisms underlying the protective effects of β-blockers on exacerbations and their consequences remain speculative, but most probably include their influence on resting tachycardia and peripheral, cardiac and neurohumoral sympathetic stress [67]. In addition, a simultaneous blockage of the β_1 pathway may protect from the adverse effects driven by excessive β_2 pathway stimulation by the increased use of bronchodilators during exacerbation [68].

Pulmonary embolism

Pulmonary embolism is a form of venous thromboembolism (VTE) and refers to obstruction of the pulmonary artery or one of its branches by a thrombus. Although dyspnoea and chest pain are the most common presenting symptoms, the clinical presentation of pulmonary embolism is variable and nonspecific [69]. In addition, pulmonary embolism may remain asymptomatic and its diagnosis may be incidental, making it difficult to establish its true epidemiology [70]. Overall, pulmonary embolism is an important cause of morbidity, hospitalisation and mortality worldwide.

In patients with underlying COPD, pulmonary embolism may mimic an exacerbation by causing an increase in respiratory symptoms. In addition, pulmonary embolism is associated with increased mortality in COPD; in a cohort of pulmonary embolism patients, the estimated relative risk of death within 1 year was 1.94 (95% CI 1.17–3.24) in those with both conditions, compared with 1.14 (95% CI 0.85–1.54) in those with pulmonary embolism only [71]. The mechanisms underlying this increased mortality were not established.

Prevalence of pulmonary embolism

An early and preliminary *post-mortem* study reported that pulmonary emboli were found in 20 out of 39 patients with any combination of terminal pulmonary emphysema, cor pulmonale or right-heart mural thrombi [72]. A case–control study from the same period investigated the incidence of pulmonary embolism or thrombosis in patients with disabling dyspnoea, a *post-mortem* diagnosis of severe pulmonary emphysema and a respiratory cause of death [73]. Among 66 necropsies fulfilling these criteria, 29% were found to have pulmonary embolism, compared with 15% in sex- and age-matched deceased controls without chronic respiratory disease.

In a small cohort of COPD patients hospitalised for an AE (n=29), 45% had incident but asymptomatic venous thrombosis, the majority of which was located proximal to the knee

and thus associated with risk of pulmonary embolism [74]. However, the relationship between the exacerbation of respiratory symptoms and thrombi or pulmonary embolism was not addressed.

Tillie-Leblond *et al.* [75] prospectively investigated the presence of pulmonary embolism in 197 consecutive patients with COPD, hospitalised for severe exacerbation of unknown origin, and reported a prevalence of 25%. Classification of exacerbations as being of "unknown origin" was defined as: 1) the absence of symptoms of a lower respiratory tract infection (increased sputum volume and/or increased sputum purulence, fever, history of cold and sore throat), 2) the absence of pneumothorax and iatrogenic intervention, 3) the presence of parenchymal condensation without fever and chills or 4) the presence of a discrepancy between clinical and radiological features and hypoxaemia severity. Since most exacerbations are accompanied by viral or bacterial airway infection [6], this study population was not representative of most exacerbations, and patients in the "pauci-inflammatory" or "eosinophil-predominant" biological clusters may have been overrepresented [8].

A study including 131 unselected and consecutive COPD patients with severe exacerbation in Turkey detected pulmonary embolism using CT pulmonary angiography (CTPA) in 18% [76]. Subsequently, the authors investigated differences in the prevalence of pulmonary embolism in patients with known (54%) or unknown (46%) origin, according to the presence of infection signs, findings for heart failure, inhalational exposure, treatment noncompliance, and evident problems in nutritional status and the patient's home care [76]. In line with the study by Tillie-Leblond *et al.* [75], pulmonary embolism was detected in 25% of patients with COPD exacerbations of unknown aetiology, while this percentage was significantly lower (8.5%) in patients with a known origin of exacerbation [76]. Importantly, in-hospital and long-term mortality were found to be significantly higher in COPD patients differentiated on the basis of having VTE [76].

Rutschmann *et al.* [77] determined the prevalence of pulmonary embolism in 123 consecutive and unselected patients admitted to the emergency department for AE of moderate to very severe COPD using a validated diagnostic strategy that included D-dimer testing. However, patients with obvious other causes for dyspnoea were excluded [77]. The overall prevalence of pulmonary embolism was 3%; although 6.2% of patients with a clinical suspicion of pulmonary embolism by the physician in charge had pulmonary embolism, it was identified in only 1.3% of those without suspected pulmonary embolism [77]. A low prevalence of pulmonary embolism (5%) was also reported in a prospective cohort of 103 hospitalised COPD patients in South Korea analysed by CTPA [78]. Patients with any specific causes of acute deterioration were excluded from the study. In contrast, 29.1% of patients in a prospective hospitalised Turkish COPD cohort had pulmonary embolism based on CTPA [79]. This prevalence did not differ among GOLD stages for airflow limitation. In another small COPD exacerbation cohort, pulmonary embolism was also investigated using CTPA, regardless of clinical suspicion; 18.4% of patients were diagnosed with pulmonary embolism [80]. Erelel *et al.* [81] observed pulmonary embolism, pulmonary embolism and deep venous thrombosis, and deep venous thrombosis only following a comprehensive diagnostic algorithm in three, two and four patients, respectively, out of a total of 56 patients hospitalised for COPD exacerbation.

In a retrospective study of critically ill patients with severe exacerbation admitted to the ICU, the incidence of pulmonary embolism was investigated by CTPA in those with high

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clinical suspicion only, consisting of 39% of the study population [82]. Within this selected group, a diagnosis of pulmonary embolism was confirmed in 17.5%. Patients with pulmonary embolism had increased ICU mortality rates and higher ICU lengths of stay compared with patients without pulmonary embolism [82].

In a large, retrospective population-based database study in Taiwan, the incidence of pulmonary embolism in a cohort of newly diagnosed COPD patients was 12.31 per 10 000 person-years compared with 3.16 per 10 000 person-years in sex- and age-matched controls, which was an ∼4-fold increased risk [83]. The relationship between risk of pulmonary embolism and exacerbations was not investigated.

Differences in study design and population, aetiology of exacerbations, diagnostic algorithms and imaging methods probably account for the large variation in prevalence of pulmonary embolism among studies (figure 2). A systematic review and meta-analysis of studies published up to April 2008 reported an overall prevalence of pulmonary embolism in exacerbations of 19.9% [84]. However, this was before many of the studies described above had been carried out, and some of the studies that were included encompassed highly selected patient groups. No studies have addressed the prevalence of pulmonary embolism in mild or moderate exacerbations and in patients with mild to moderate airflow limitation. In addition, the possible role of acute or chronic pulmonary embolism in COPD patients with a "frequent-exacerbator" phenotype [5] requires further exploration.

Risk factors for pulmonary embolism

Chen *et al.* [83] identified younger age and the presence of comorbid conditions as independent risk factors for pulmonary embolism in COPD patients registered in a health insurance research database. The relationship with exacerbations was not addressed. Several studies have investigated factors associated with the presence of pulmonary embolism in

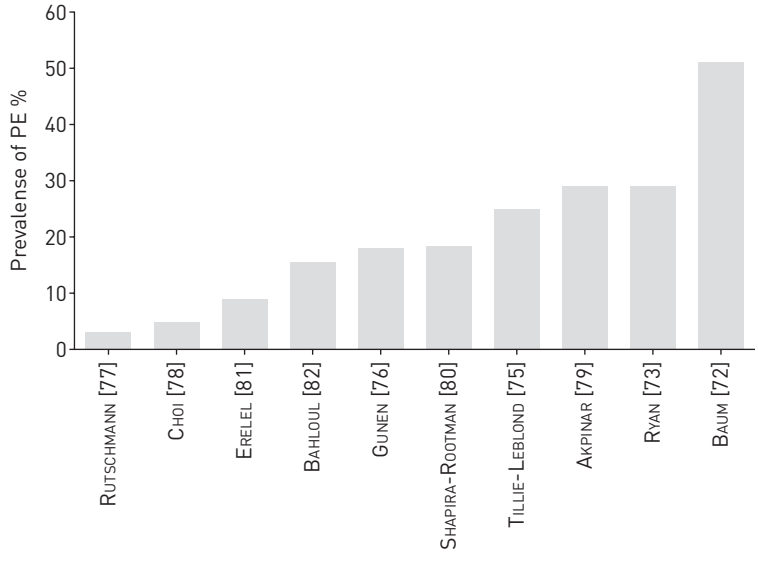

Figure 2. Prevalence of pulmonary embolism (PE) in COPD exacerbations across studies. The x-axis shows first author [ref.] for each study.

exacerbations [75, 76, 78, 79, 85]. Clinical symptoms, including a change in dyspnoea, thoracic pain, haemoptysis, tachycardia and lower extremity oedema, were not associated with pulmonary embolism in patients with severe exacerbation of unknown origin [75]. In addition, arterial blood gas values and the need for long-term oxygen therapy were not related to pulmonary embolism in this population. However, a reduction in $P_{a}CO_2$ of ⩾5 mmHg from baseline values, a history of thromboembolism and malignant disease were associated with pulmonary embolism [75]. In unselected patients, the absence of symptoms of airway infection, elevated plasma D-dimer levels [78], obesity and lower limb asymmetry [79] were significant predictors of pulmonary embolism. In patients with known and unknown aetiology of exacerbations, female sex, chest pain, syncope, hypotension, atrial fibrillation and evidence for right-heart failure were identified as clinical predictors of VTE including pulmonary embolism [76]. In COPD patients with a clinical suspicion of pulmonary embolism, clinical, radiography and arterial blood gas studies did not differentiate between exacerbation and pulmonary embolism [85]. Several studies have indicated that the prevalence of pulmonary embolism is not related to the degree of airflow limitation [76, 79, 86].

Kim *et al.* [86] investigated risk factors for VTE in 10 237 clinically stable moderate to severe COPD patients by comparing those with a self-reported history of this condition (4.3%) with those without. In a multivariate analysis, increasing body mass index, reduced functional capacity, previous pneumothorax and a history of cardiovascular disease increased the odds for VTE [86].

Despite differences in outcomes, no differences in clinical or biochemical variables were observed between patients with and without pulmonary embolism admitted for mechanical ventilation for severe exacerbation [82].

Based on the available literature, it is clear that the diagnosis of pulmonary embolism in patients with exacerbations is difficult to predict. While risk factors for pulmonary embolism in COPD may be largely comparable to those in other populations, the diagnosis should especially be considered in patients with high body mass index with reduced physical activity presenting with increased dyspnoea in the absence of infectious symptoms, relative hypocapnia, a previous history of VTE/pulmonary embolism, or malignancy. In addition, the distribution of D-dimer as a test in conjunction with clinical probability for ruling out VTE is similar in patients with and without COPD [87]. Moreover, the prevalence of pulmonary embolism in patients with COPD does not appear to be increased compared with that in other populations [87]. However, in COPD patients who presented with pulmonary embolism, the risk for pulmonary embolism recurrences and fatal pulmonary embolism was significantly increased compared with those who presented with venous thrombosis, emphasising the need for efficient secondary prevention [88].

Clinical implications of pulmonary embolism

Based on the low prevalence of pulmonary embolism in the total exacerbating COPD population, routine investigation of patients presenting with COPD exacerbations is not warranted. In patients with suspected pulmonary embolism and underlying COPD, the diagnostic value of the clinical probability estimate, D-dimer assay and CTPA and the reproducibility of pulmonary angiography were not different from those in non-COPD subjects [89]. In addition, recommendations regarding pharmacological thromboprophylaxis are not different for hospitalised COPD patients than for other patients in the hospital.

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Differential diagnosis and phenotyping of COPD exacerbations

Exacerbations of COPD are associated with substantial morbidity and mortality [6]. The heterogeneous nature of the inflammatory pathways and aetiologies of exacerbations remain incompletely understood. In order to stimulate the identification of specific patterns of exacerbations both within and between individual patients, and to study the aetiology of these patterns and investigate their associations with long-term outcomes, MacDonald *et al.* [90] proposed an approach to clinically phenotype them, using the ABCDEFG-X (airway viral infection, bacterial infection, co-infection, depression/anxiety, embolism, failure (cardiac or lung integrity), general environment, X (no specific cause identified)) model. Each component of the model can cause symptoms that meet the definition of an exacerbation [51]. Until more personalised and improved interventions to prevent and treat exacerbations become available, consideration of the diagnoses in the proposed acronym may support the consideration of differential diagnosis in respiratory practice. Although an evidence-based diagnostic and treatment algorithm accounting for the heterogeneity of exacerbations has not yet been established, healthcare professionals involved in the management of these patients should consider alternative aetiologies of increased dyspnoea in those patients who do not respond to traditional treatment with bronchodilators, antibiotics and systemic corticosteroids.

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Disclosures: None declared.

 https://doi.org/10.1183/2312508X.10016316

Asthma: treatment and prevention of pulmonary exacerbations

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The typical management plan for treatment for an exacerbation of asthma has mostly remained unchanged for 20 years, with systemic steroids and bronchodilators remaining the unavoidable cornerstones for treatment. Deaths due to asthma are rare occurrences in the hospital setting, which does not provide an incentive for improvements in treatment management. However, it is thought that ~50% of asthma deaths overall may be preventable. This has stimulated new research into the use of biologics, resulting in a promising new era where management strategies are likely to shift dramatically.

Cite as: Charriot J, Volpato M, Sueh C, *et al*. Asthma: treatment and prevention of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 129–146 [https://doi.org/10.1183/2312508X.10016416].

The prevention and treatment of asthma are such vast areas of research that this chapter can only summarise what has been already been described in other reviews and in the Global Initiative for Asthma (GINA) guidelines [1]. Reducing exacerbation rates is now seen as the ultimate goal of asthma management, as exacerbations encompass most of the present and future asthma risks [2–4]; therefore, this chapter will focus mainly on current and future targeted strategies to achieve this goal.

Exacerbations are the hallmarks of the natural history of asthma. The definition of an exacerbation and its assessment has been reviewed elsewhere [2]; the definition, severity and impact of exacerbations of asthma have also been discussed elsewhere in this *Monograph* [5]. Asthma diagnosis is frequently evoked around these events, which are mostly triggered by viral infections and/or concomitant allergen exposure [6, 7], prolonged and/or massive allergen exposure, or a combination of both. Repeated assessments of the level of asthma control are recommended, as this is a good predictor of subsequent

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

exacerbation episodes [8]. However, it should be noted that, although an exaggerated duration of these episodes is suggestive of asthma, this also indicates a failure of mechanisms implicated in the resolution of inflammation [9].

The burden of asthma is now understood as the result of symptoms and treatment side-effects, and this is particularly true with increasing severity [10–12]. Indeed, severity is highly associated with frequently recurring exacerbations [13–17], which often require additional treatments with imperfect safety profiles.

Biologics and other innovations have the potential to greatly modify the asthma paradigm [18–21], and it seems that the goal of reducing the number of asthma exacerbations towards zero will be achievable for those who can access and follow these novel treatments.

Treatment of asthma exacerbations

Assessment and nonpharmacological interventions

Whether an asthma exacerbation has the potential to be life-threatening is a cause for concern for both patients and clinicians [14]. Assessing the immediate and short-term risks requires active and rapid clinical examination, concomitant with the initiation of management [22]. Identification of a convincing cause can be insightful for immediate management, and this area is progressively improving. For example, identifying a viral infection at the time of admission in children is a very strong predictor of emergency department readmission, and can be sufficient to change local policy [23].

The decision of whether or not to admit a patient evaluated in the emergency department is highly variable, and the criteria are subjective and not consistently considered. Outpatients are usually managed with very limited or without any paraclinical examination.

Although there is little robust evidence of the benefits of nonpharmacological interventions, especially in children [24], intuitive relevant advice is generally accepted in the community. A number of studies that have analysed the effects of nonpharmacological interventions are described in table 1.

Pharmacological interventions

Bronchodilators and steroids are the cornerstones of exacerbation management.

Bronchodilators

Rapid-onset bronchodilators have been known for thousands years in this setting in the form of epinephrine-containing herbal preparations [44]. Some of the new β_2-agonists are characterised by a longer duration of action, but most also combine rapidity of action. Formoterol was approved for use in combination with an inhaled corticosteroid (ICS) in a maintenance and reliever therapy (MART) strategy, where it reduces the risk of exacerbation [8, 45], but other β_2-agonists have not been tested or approved for this indication. Excellent bioavailability indicates no theoretical superiority of systemic administration over inhalation, but this point remains unclear, especially in highly inflamed and constricted airways that may also be subject to mucus plugging. Whether inhalation should utilise a nebuliser or an established inhaler device has been debated, and wide

 https://doi.org/10.1183/2312508X.10016416

Table 1. Summary of the available evidence for nonpharmacological interventions in the treatment of ongoing asthma exacerbations

First author [ref.]	Nonpharmacological intervention	Comments
Ducharme [23], Beasley [25], Abramson [26, 27], Alvarez [28], ATS [29]	Avoid smoking, additional allergen exposure, stress and excessive emotions, occupational noxious exposure, indoor and outdoor excessive pollution, strong exercise, β-blockers and β_2-agonist overuse	Very little evidence during exacerbations
None	In susceptible patients, avoid NSAIDs and aspirin	No evidence
Anderson [30], Marchette [31], Kondo [32]	Strategies aimed at facilitating mucus clearance, including "more than usual" daily water intake and hydration if admitted to hospital	Indirect evidence
Greening [33], Brandão [34], Kera [35]	Choose facilitating position and avoid excessive physiotherapy	Little evidence
Zöller [36]	Consider gastric ulcer and thromboembolic preventions if admitted, especially in the ICU	Indirect evidence; nothing related to gastric ulcers
DaCruz [37], Smith [38], Singhi [39], Rodrigo [40], Kowal [41]	Reduce potentially harmful treatment side-effects (*e.g.* hypokalaemia, hypomagnesaemia)	Clear evidence for potassium
None	Do not stop controlling comorbidities (*e.g.* CPAP for sleep apnoea, insulin in diabetes, antidepressants)	No evidence
Brandão [34]	Oxygen and helium/oxygen supplementation	In selected situations only
Pallin [42]	Noninvasive ventilation in the ICU	Controversial
Brogan [43]	ECMO for near-fatal episodes	Many case reports

NSAID: nonsteroidal anti-inflammatory drug; CPAP: continuous positive airway pressure; ECMO: extracorporeal membrane oxygenation.

discrepancies among patients may exist in terms of the most effective method. Lung deposition depends on many factors, but nebulisers are probably superior to inhalers in an emergency situation. It is likely that fear of critical mistakes explains why nebulisers are used routinely in the emergency room and after admission or at home. The half-life of these short-acting β_2-agonists (SABAs) is 4–6 h, which is the current basis for dosing. Continuous administration of β_2-agonists is not superior to regular inhalations, and there is little evidence to support their administration intravenously [46].

The safety of β_2-agonists is a cause for concern. Immediate off-target side-effects include tachycardia and tremor. Drug accumulation and medium- to long-term side-effects are less well known, but these are important issues to address. Hypokalaemia, increased serum lactate/acidosis and tachycardia are important conditions for torsade de pointes and other ventricular arrhythmias, the risk of which may also be increased by concomitant high-dose steroid administration [39, 47–49]. Increased production of lactic acid is another side-effect of concern [47].

It is noteworthy that β_2-agonists have continued to be surveyed since the 1990s after two epidemics of asthma led to increased asthma mortality in New Zealand [25]. It remains

unclear when use of β_2-agonists becomes "overuse", and there is only poor quality evidence to inform guidelines. In the emergency room and during hospital stays, high doses of β_2-agonists are frequently administered and maintained throughout the stay, irrespective of any specific measurement. Regional heterogeneities may also exist. For example, intravenous salbutamol is frequently used in France, whereas this is rarely done elsewhere.

Anticholinergics are widely used in association with β_2-agonists, as this has been demonstrated to have a positive effect during the first days of admission [50]. Outpatient management of asthma exacerbations has not been tested. Long-acting muscarinic antagonists have not been tested during the acute phase of exacerbations, although they have the potential to offer greater levels of bronchodilation. Off-label use of nebulised short-acting muscarinic antagonists (SAMAs) is infrequently seen, and expected safety concerns have not been addressed to date [50].

Pharmacogenetic studies have identified single nucleotide polymorphisms associated with worse asthma outcomes [51], but no clear-cut evidence supports the benefit of performing such a screening in at-risk populations [52, 53]. Paradoxically, β_2-agonist-induced loss of lung function has been explored in COPD, but these data could not be extended to asthma at that time [54].

Approved SABAs and SAMAs for the treatment of asthma exacerbations are summarised table 2.

Steroids

Asthma exacerbations related to viral infections and/or other epithelial injuries are mostly attributed to excessive type 2 inflammation [63]. The genomic and nongenomic effects of steroids probably represent a double-edged sword of steroid use in asthma exacerbation. Although alarmins and type 2 innate lymphoid cells are classically steroid resistant, it seems that downstream cytokines are more or less steroid sensitive [64–66], resulting in the expected decrease in inflammation of the eosinophilic airway and inhibition of the release of preformed mediators from mast cells recruited near the smooth muscle bundles [67, 68]. Other benefits from steroids may include decreased airway wall oedema and bronchial vessel size, whereas decreased small airway mucus plugging probably results from cytokine inhibition [18, 69, 70]. Because major basic protein, released from eosinophilic granules, can interfere with the smooth muscle tone regulator at the M2 receptor [71, 72], steroids

Table 2. Short-acting β_2-agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) approved for the treatment of asthma exacerbations

Drug	Existing route of delivery	Class	First author [ref.]
Albuterol sulfate (salbutamol sulfate)	DPI with/without spacer; pMDI (HFA); nebuliser (inhalation solution)	SABA	Colacone [55], Drazen [56]
Ipratropium bromide (add-on therapy)	Nebuliser	SAMA	Rodrigo [57], Griffiths [58] (children)
Levalbuterol	pMDI (tartrate, HFA); nebuliser (hydrochloride inhalation solution)	SABA	Nelson [59], Milgrom [60] (children)
Terbutaline sulfate	DPI with/without spacer; nebuliser (inhalation solution)	SABA	Wolfe [61], Rufin [62]

DPI: dry-powder inhaler; pMDI: pressurised metered-dose inhaler; HFA: hydrofluoroalkane.

 https://doi.org/10.1183/2312508X.10016416

are thought to improve bronchodilator effects in this inflammatory context. Molecular synergy through intracellular cAMP response element-binding protein (CREB) inhibition may also result in a better steroid response induced by β_2-agonists, although these mechanisms could not be clearly demonstrated *in vivo* [73, 74].

Pharmacogenetic heterogeneity and/or epigenetic modifications of biological targets of steroids have also been reported; for example, cigarette smoke is known to affect histone deacetylase/histone acetyltransferase imbalance and decrease access to steroid sites of action [67, 75].

There are concerns about the inconsistent assessment of severity of an asthma exacerbation and the requirement for systemic steroids. Inappropriate use of steroids appears to be frequent, but this is still to be established. The ideal dose and length of steroid use in this context have not been addressed, but it is likely that currently used doses are too high [76], although an insufficient length of exposure to steroids may result in treatment failure and the need for emergency department readmission [77]. The side-effects of systemic steroids are well known. Short and repeated bursts of steroids potentially expose different side-effects compared with long-term administration. Monitoring the onset of acute side-effects, such as diabetes or hypertension, is outside current guidelines in the absence of evidence, although these adverse events can be serious. The best regimen and best drug to use is complex to identify, and no clear superiority has been demonstrated [76].

Inhaled steroids are intended to spare steroid exposure in asthma treatment maintenance [78]. This topical treatment may provide local concentrations sufficient to control airway inflammation, decrease exacerbation rates and save asthma lives. Strategies such as MART with variable ICS doses have shown better control of airway inflammation and airway constriction in a time-adapted manner, indicating that increasing the local ICS dose may have the potential to avoid exacerbations becoming severe [8, 45, 79, 80]. Unexpectedly, ICSs are unable to sufficiently control inflammation in the context of severe asthma exacerbations, suggesting systemic signalling that is too strong, probably involving the bone marrow production of leucocytes [81]. In children, ICSs may also be beneficial in the context of mild exacerbations [82, 83].

Other potential drugs for managing asthma exacerbations

Magnesium sulfate and a helium/oxygen mixture have been tested in near-fatal episodes of asthma exacerbations. Magnesium sulfate is thought to act through a complementary pathway for relaxing smooth muscle cells and is used in the ICU [84, 85], but regional heterogeneities in the use of this method exist. A helium/oxygen mixture is thought to improve the laminarity of the airway flux within the airways and improve the deposition of inhaled drugs. This treatment has mostly been restricted to patients admitted to the ICU, with limited evidence of insufficient quality [86].

Antibiotics are widely used, despite limited evidence of bacterial infection [87]. Ketolides, but not other macrolides, have demonstrated specific improvements potentially related to unexpected nonantimicrobial effects [88, 89]. Their ability to interfere with steroid metabolism and artificially increase steroid bioavailability has been suggested [90].

In extreme cases requiring mechanical ventilation, ketamine in children [91] and sevoflurane [92] have been shown to be candidate options.

It is noteworthy that theophylline has been used in many cases and can still be used in the absence of alternatives. Although the evidence is sparse and side-effects are a serious cause for concern, it should be kept in mind as an available and cheap option [92].

Events of special interest

Viruses are now well established culprits for exacerbating asthma. Antiviral treatments are not routinely available, but interesting data have been reported recently supporting this concept [93] and a larger trial is expected.

There is now increasing evidence linking increased lung pressure and spontaneous pneumothorax or pneumomediastinum. Because seasonality has been clearly observed, with peaks occurring after brutal atmospheric pressure changes for these events, the link with episodes of diagnosed or undiagnosed asthma exacerbation now looks credible [94].

Preventing early relapses

Failure of management of an asthma exacerbation is infrequently seen in the emergency department, but when it occurs, inadequate behaviour in the days following discharge have been identified in these patients [77, 95]. Chapman *et al.* [77] demonstrated the clear benefits of a prolonged systemic steroid intake, whereas others have highlighted the critical importance of starting a maintenance inhaled treatment [96]. A short-term review by any healthcare provider after such an episode has the potential to reduce such relapses.

Steroids are given because of their anti-inflammatory effects. In these situations, genomic effects are thought to be the most adapted, reducing the production of pro-inflammatory cytokines such as IL-5. Taking advantage of this observation, Nowak *et al.* [97] showed a significant benefit of a single administration of benralizumab at the time of an exacerbation in preventing a subsequent recurrence when compared with placebo.

Shortening exacerbations of asthma

Defective antiviral defence is now regarded as a feature of asthma associated with frequent exacerbations. Inadequate interferon production has been shown as the basis for this maladapted antiviral response [98, 99]. Thus, early administration of inhaled interferon may reduce the duration of an exacerbation if started within the first hours of symptoms. This scheme is similar to the anti-influenza benefits of oseltamivir [100]. A phase II study showed promising results with an excellent safety profile, especially in severe asthma patients, but concerns related to poor specificity of the symptoms and the absence of clear-cut biomarkers were raised [93]. Discussion of the prevention of respiratory syncytial virus infection in children at high risk is outside the scope of this chapter.

Lipoxins and other lipid mediators have the potential to reduce the duration and severity of asthma exacerbations by promoting the resolution of inflammation. Pre-clinical and *in vitro* data support these views and clinical trials are expected soon [9].

Patient-reported outcomes and psychological perspectives

What is the burden of an exacerbation and treatment? How can we manage admission and the need for unscheduled visits? How frightening are near-fatal episodes [101]? There is

 https://doi.org/10.1183/2312508X.10016416

suspicion around asthma exacerbations because surveys have demonstrated the impact of poor adherence, which may have a negative effect on patient–doctor relationships [102–104].

Patients are unlikely to use the word "exacerbation", and a lack of knowledge of the correct terminology might be important in patients' reports of their symptoms. Perceptions of symptoms [105], alexithymia [106], anxiety and hyperventilation are potential causes for concern [107].

Preventing asthma exacerbations in the biologics era

Assessment and existing strategies

GINA guidelines rely on escalation/de-escalation of five severity steps [1]. Interestingly, the level of asthma control assessed in the clinic is an essential indicator of the need for a change of step. Asthma control refers to symptoms and future risk, which includes exacerbations. Potentially, exacerbations are now regarded as the primary outcome in managing asthma, as they encompass most of the asthma risk (decline in lung function, emergency/death, exposure to high-dose systemic steroids and other medications) [1].

Currently, the exacerbation risk is based mostly on a previous history of exacerbations, but other known risk factors need to be taken into account [108, 109]. Blood eosinophil count is a biomarker related to the frequency of asthma exacerbation rates in large asthmatic cohorts [110]. How this translates individually is not clear at this stage. Scores of asthma control have been shown to predict the onset of an exacerbation [111]. Existing strategies aimed at avoiding exacerbations can be built up towards asthma treatment as a whole, and include not only pharmacological support but also environmental control and educative actions.

Recently, the 13-valent conjugate antipneumococcal vaccine received approval in severe asthma patients (and in COPD patients), although a specific trial has only been reported to date in asthmatic children and adolescents [112].

Nearly all drugs currently in development are following a strategy of exacerbation rate reduction in frequent-exacerbator asthmatics [18]. In general, these controlling drugs are aimed at reducing exaggerated airway inflammation in response to any trigger in order to return to the nonasthmatic level of inflammation and subsequently to a more adapted response. Table 3 summarises the results of studies showing reduction of exacerbation rates of the tested drugs *versus* placebo. It is noteworthy that, outside specific clinical situations such as allergic bronchopulmonary aspergillosis, specific antifungal therapies in sensitised patients failed in two large trials [147, 148]. Specific details on eosinophilic granulomatosis with polyangiitis are not given here.

Managing comorbidities to reduce asthma exacerbations

The use of bariatric surgery for obesity is probably one of the more convincing pieces of clinical evidence that managing one comorbidity can improve asthma [150]. Although improvements are not consistent and prevention of exacerbations not definitely clear, this type of intervention might be considered in obese asthma patients with frequent exacerbations, as a 50% reduction in emergency department visits or hospitalisation for exacerbations was described in one study [151].

Table 3. Current and future therapeutic options to prevent asthma exacerbations

mAB/other drugs	Biological target	Targeted population	Study duration	Reduction of exacerbation rate (*versus* placebo)	Comments	First author [ref.]
Mepolizumab	IL-5	Severe eosinophilic with/without steroid dependent; frequent exacerbator	6–12 months	32–53%	*s.c.* monthly; marketed	Bel [113], Liu [114], Ortega [115], Pavord [116]
Benralizumab	IL-5R	Severe eosinophilic with/without steroid dependent; frequent exacerbator	12 months	23–41%	*s.c.* every 2 months	Castro [117], Bleecker [118], FitzGerald [119]
Reslizumab	IL-5	Severe eosinophilic with/without steroid dependent; frequent exacerbator	12 months	54–57%	*i.v.* monthly; marketed	Castro [120, 121]
Dupilumab	IL-4Rα	Inadequately controlled moderate to severe, ⩾1 exacerbation	12 months	70–87%	*s.c.* every 2 weeks	Wenzel [122, 123]
Lebrikizumab[#]	IL-13	Severe, OCS dependent	12 months	NS	*s.c.* monthly; patients stratified by baseline periostin level	Corren [124], Hanania [125, 126]
Tralokinumab	IL-13	Severe; frequent exacerbator	12 months	NS	*s.c.* monthly; additional improvements in pre-bronchodilator FEV_1, ACQ-6 and AQLQ(S) in high baseline DPP4 subgroup	Brightling [127], Piper [128]
Fevipiprant (CRTh2 antagonist)	PGD2R	Severe; frequent exacerbator	12 weeks	NA	Oral; other PGD2R antagonists failed	Gonem [129], Miller [130]
GATA3 DNAzyme	T2 cells	Allergic	3 months	NA	Ongoing	Homburg [131]; Krug [132]
Anti-IL-33	ST2-positive cells	Too early	Too early	Too early	Too early	

Continued

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Table 3. Continued

mAB/other drugs	Biological target	Targeted population	Study duration	Reduction of exacerbation rate (*versus* placebo)	Comments	First author [ref.]
Anti-TSLP	TSLP alarmin	Too early	Too early	Too early	Too early	Gauvreau [133], ClinicalTrials.gov number NCT02698501
Omalizumab	IgE	Severe perennial allergic; frequent exacerbator	12 months	25–46%	*s.c.*; IgE; marketed	Bousquet [134], Humbert [135], Hanania [136], Normansell [137], Teach [138], Busse [139]
HDM-SLIT	Treg	Severe HDM allergic asthma	6 months after ICS withdrawal	30%	Daily oral	Virchow [140]
Anti-IL-17	IL-17RA	Inadequately controlled, moderate to severe	12 weeks	NA	*s.c.* every 2 weeks; benefits in high-reversibility group	Busse [141]
Infliximab and etanercept	TNF	Inadequately controlled, moderate to severe	6–10 weeks	No change	*i.v.* or *s.c.* twice a week	Holgate [142], Morjaria [143], Berry [144]
Masitinib	c-kit	Severe oral corticosteroid dependent	16 weeks	No change		Humbert [145]
Antifungal	*Aspergillus*	Severe *Aspergillus fumigatus*-allergic asthma	Itraconazole 32 weeks; voriconazole 3 months	No change	Oral	Denning [146], Agbetile [147]
Azithromycin, macrolides	Unclear	Neutrophilic severe asthma	6 months	No change	Oral	Brusselle [148], Kew [149]

mAB: monoclonal antibody; *s.c.*: subcutaneous; IL-5R: IL-5 receptor; *i.v.*: intravenous; IL-4Rα: IL-4 receptor α; OCS: oral corticosteroid; NS: not significant; CRTh2: chemoattractant receptor-homologous molecule expressed on TH2 cells; PGD2R: prostaglandin D2 receptor; ACQ-6: Asthma Control Questionnaire-6; AQLQ(S): Standardised Asthma Quality of Life Questionnaire; DPP4: dipeptidyl peptidase-4; NA: not available; too early: phase II trial results only (no phase III trial results yet); TSLP: thymic stromal lymphopoietin; HDM-SLIT: house dust mite sublingual allergen immunotherapy tablet; Treg: T-regulatory cell; IL-17RA: IL-17 receptor A. #: lebrikizumab development has now been stopped.

In contrast, disappointing issues have been reported with proton pump inhibitors in gastro-oesophageal reflux disease [152–155], so reflux cannot be considered a consistent therapeutic axis for preventing asthma exacerbations. Similarly, hormonal substitution for pre-menstrual asthma was seen as promising in women described periodic symptom worsening, but did not significantly improve the Asthma Quality of Life Questionnaire score [156]. This hypothesis remains unaddressed, and interest in the field has decreased significantly.

Interesting debates related to whether rhinitis/rhinosinusitis management may improve asthma outcomes are ongoing [157], but few trials have assessed the benefits of treating the nose on asthma exacerbation rates. Nasal and sinonasal surgery benefits are complex to assess outside open-label or real-life studies, and it is difficult to evaluate systematically the exact place and timing in patients with the aim of preventing exacerbations.

The potential benefits of managing apnoea, diabetes, heart failure and psychological/psychiatric conditions are unknown, because patients with such comorbidities are usually excluded from more or less all clinical trials [158].

Allergen avoidance is extremely complex to indicate, manage and check, and thorough, very focused and specific investigations have mostly failed in reducing asthma exacerbation rates [159, 160].

The management of asthma exacerbations in the elderly is of concern when it comes to comorbidities [161]. Beyond the issue of the diagnosis itself, because age is thought to be a factor in COPD, is reversibility needed to diagnose asthma in this population? Is air trapping in elderly people really pathological? Is there an underlying cardiopathology? However, the risk of polypharmacotherapy remains the main concern to deal with [162]. SABA nebulisations should be used with great caution due to the potential cardiac side-effects, whereas the decision to expose the patient to systemic steroids is much more complex when considering diabetes, osteoporosis, skin bruising and other issues, which are common comorbidities in the elderly. Moreover, preventing exacerbations may become difficult if the handling of inhalation devices is not suitable for people with motor and/or psychological problems. Frequently, asthma treatment has been seen as optional in elderly people because the idea that asthma progressively decreases with age is common. Whether biotherapies will be an opportunity to target this population, who are usually excluded from clinical trials, is a matter for future research.

Future educative and therapeutic strategies

Asthma management plans devised by multidisciplinary therapeutic education teams, with or without the help of modern communicating tools such as web-based sites or mobile phone applications, are certainly useful in candidates who volunteer for such interventions [163–166]. Unfortunately, these interventions have mostly failed to have much impact on asthma exacerbations, and overall asthma control surveys in the general population have been disappointingly stable over the years [167]. This is probably because therapeutic education programmes face the challenge of reaching the most at-risk patients who frequently remain outside these management pathways. New ideas are needed to overcome these issues. Because monoclonal antibodies and other interventions are usually expensive, various scenarios have been proposed.

 https://doi.org/10.1183/2312508X.10016416

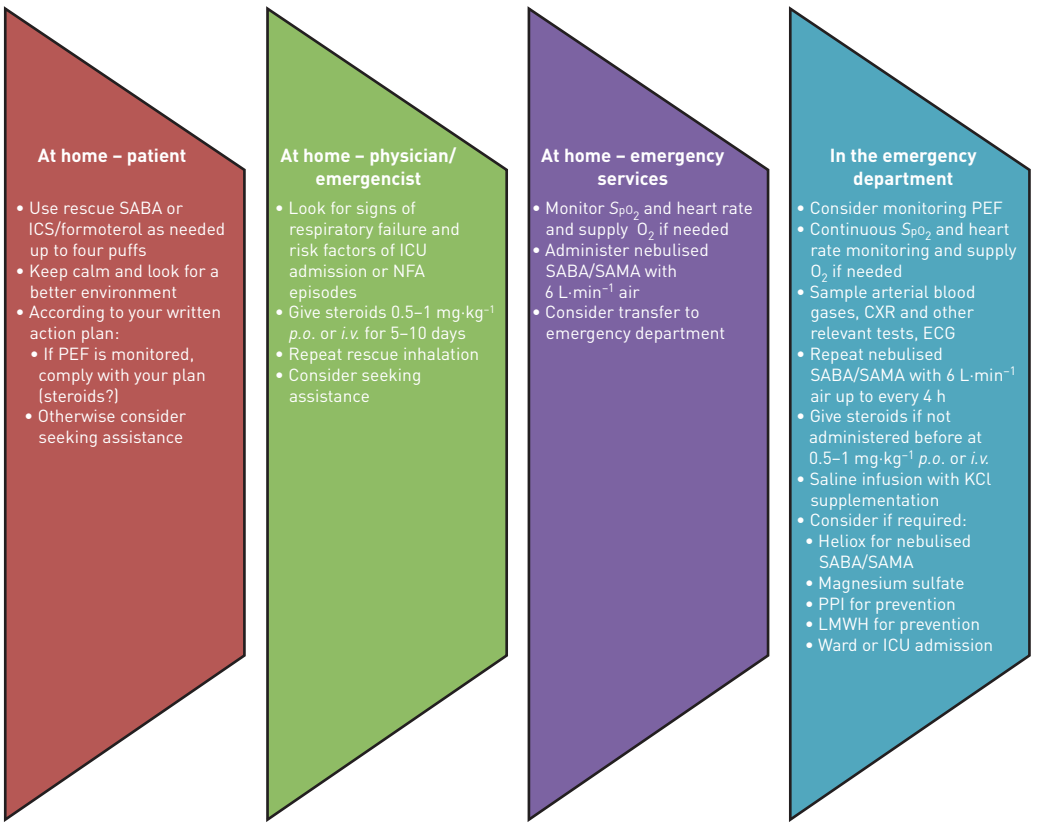
At home – patient
• Use rescue SABA or ICS/formoterol as needed up to four puffs
• Keep calm and look for a better environment
• According to your written action plan:
• If PEF is monitored, comply with your plan (steroids?)
• Otherwise consider seeking assistance
At home – physician/ emergencist
• Look for signs of respiratory failure and risk factors of ICU admission or NFA episodes
• Give steroids 0.5–1 mg·kg^{-1} *p.o.* or *i.v.* for 5–10 days
• Repeat rescue inhalation
• Consider seeking assistance
At home – emergency services
• Monitor S_{pO_2} and heart rate and supply O_2 if needed
• Administer nebulised SABA/SAMA with 6 L·min^{-1} air
• Consider transfer to emergency department
In the emergency department
• Consider monitoring PEF
• Continuous S_{pO_2} and heart rate monitoring and supply O_2 if needed
• Sample arterial blood gases, CXR and other relevant tests, ECG
• Repeat nebulised SABA/SAMA with 6 L·min^{-1} air up to every 4 h
• Give steroids if not administered before at 0.5–1 mg·kg^{-1} *p.o.* or *i.v.*
• Saline infusion with KCl supplementation
• Consider if required:
• Heliox for nebulised SABA/SAMA
• Magnesium sulfate
• PPI for prevention
• LMWH for prevention
• Ward or ICU admission

Figure 1. Different management strategies for an asthma exacerbation, according to context. SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; PEF: peak expiratory flow; NFA: near-fatal asthma; *i.v.*: intravenous; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; SAMA: short-acting muscarinic antagonist; CXR: chest autoradiograph; KCl: potassium chloride; heliox: helium/oxygen mixture; PPI: proton pump inhibitor; LMWH: low-molecular-weight heparin.

https://doi.org/10.1183/2312508X.10016416

Bronchial thermoplasty has been developed, and successfully demonstrated a significant reduction in exacerbation rates in severe asthma patients [21, 168, 169]. Guidelines still recommend that bronchial thermoplasty is performed in expert centres in clinical trials. It is possible that just three sessions might reach the disease modifier status [168], and this point should be carefully surveyed.

Pre-seasonal omalizumab use in the run-up to autumn is a clever option tested with a very elegant design in a clinical trial where it significantly reduced exacerbation rates in children and adolescents, but only if they already experienced such episodes during this period [138]. It should be noted that this study design was superior to an ICS burst [138].

ICS withdrawal is a good way to indicate not only that the intervention is modifying the natural history of the disease, but also to fix troubles with poor adherence. Dupilumab and a house dust mite sublingual allergen immunotherapy tablet were both successfully tested in this regard [122, 140], whereas ICS withdrawal is significantly achievable with omalizumab [137]. Indeed, most patients who gained total control, known as "superresponders", with any of these interventions may benefit from innovative ways of management. A recent report provided an example that took advantage of new biologics efficacy, general practitioner–specialist–patient networking, MART strategies as needed and directly observed treatment benefits [170].

Conclusion

Treatment for an exacerbation of asthma has mostly remained unchanged for 20 years, and a typical management plan is shown in figure 1. Systemic steroids and bronchodilators are still unavoidable cornerstones of treatment. Because asthma death is a rare event in the hospital, few improvements are expected. However, because around half of asthma deaths in general may be preventable [171], this has stimulated new research into the use of biologics with a new era where management strategies are likely to shift dramatically.

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Disclosures: P. Chanez reports receiving grants and personal fees from Almirall, BI, Centocor, GSK, MSD, AstraZeneca, Novartis, Teva, Chiesi and Schering Plough, outside the submitted work. A. Bourdin has received the following during the conduct of the study: grants and personal fees from AstraZeneca and Boehringer Ingelheim; and personal fees from GSK, Novartis, Roche, TEVA and Chiesi.

 https://doi.org/10.1183/2312508X.10016416

Chapter 11

COPD: treatment and prevention of pulmonary exacerbations

Nicolas Roche

COPD exacerbations are frequent events that have major short- and long-term impacts on both patients and society, making their treatment and prevention crucial issues. Recognising exacerbations in order to initiate early treatment is the first step of their management, followed by determining whether the patient can be managed at home or should be referred to the hospital. Exacerbation treatments rely on bronchodilators, antibiotics and corticosteroids, as well as oxygen therapy and ventilatory support if required. Prevention of exacerbations is based on pharmacological agents (mostly inhaled treatments, *i.e.* long-acting bronchodilators and corticosteroids) that should be prescribed gradually based on the patient's individualised categorisation, and on nonpharmacological measures, including smoking cessation, rehabilitation, education and integrated care. Efforts should also be directed at improving guideline implementation and standards of care in this area, to offer all patients a personalised approach.

Cite as: Roche N. COPD: treatment and prevention of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 147–166 [https://doi.org/10.1183/2312508X.10016516].

COPD exacerbations represent a major burden to both patients and society, both during the "acute phase" and in the long term. Therefore, both their treatment and prevention are of key importance and represent a major topic in guideline documents on COPD [1–3]. The purpose of this chapter is to provide an overview of recent evidence and current treatment trends, and to pinpoint remaining areas of debate.

Treating COPD exacerbations

The treatment of COPD exacerbations aims to decrease the risk of poor outcomes and to shorten recovery time, thereby decreasing immediate morbidity, mortality, and direct and indirect costs. In general, the sequence of exacerbation management can be summarised as follows: identify the exacerbation, assess the severity and choose the care setting, implement the correct medications and nonpharmacological therapy, monitor, decide and organise discharge (if hospitalised), and plan the follow-up and preventative measures. In clinical

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

trials and guidelines, exacerbations are usually categorised as mild (self-managed), moderate (requiring antibiotics and/or corticosteroids) or severe (hospitalised) [2]. An additional "very severe" level is sometimes added for patients requiring ICU admission and/or ventilatory support. This classification scheme is appropriate for retrospective severity assessment, but not to categorise the patient status before any treatment decision is made.

Identification and assessment

Acute respiratory episodes in patients at risk as an opportunity for targeted case finding

When facing a patient with an acute lower respiratory episode and no known underlying respiratory disease, the medical history should be taken carefully to assess risk factors, previous chronic respiratory symptoms and acute episodes, and current symptoms. If these include dyspnoea, the diagnosis of uncomplicated acute bronchitis should be reconsidered, and pneumonia or exacerbation of a chronic underlying respiratory (or cardiac) disease needs to be envisaged. If risk factors for COPD are reported (*e.g.* smoking, occupational exposures), this diagnosis needs to be considered, explored and treated [2]. The issues here are: 1) to treat the exacerbation appropriately (note that, following several guidelines for respiratory physicians and general practitioners, as well as a recent Cochrane review, bronchodilators would not be routinely used if the patient is wrongly considered as suffering from an uncomplicated acute bronchitis) [4–6] and 2) to take this opportunity to engage the patient in an active targeted case-finding approach. Spirometry could be performed during the acute phase if it is available, if the symptoms are not too severe and if the physician believes that the patient would not come back for follow-up assessment including spirometry. In any case, spirometry needs to be performed or repeated after the patient has returned to steady state. Unfortunately, surveys have found that acute respiratory episodes are infrequently taken as opportunities for active case finding [7].

Early identification and treatment of COPD exacerbations

It has been shown that early identification and treatment of exacerbations is associated with improved outcomes, including better health-related QoL, reduced hospitalisation rates and shortened recovery time [8]. Enhancing exacerbation recognition by healthcare professionals and patients requires appropriate education; otherwise about half of exacerbations are not identified, leading to poorer outcomes [9, 10]. More details on this topic are provided later in this chapter.

Assessing exacerbations to choose the right setting for care

Guideline documents propose criteria to guide orientation decisions, such as those presented in table 1. Questions to be addressed are whether the patient should be assessed in the hospital, whether they should be admitted, whether ICU admission should be considered and whether ventilatory support should be provided. The last factor may not be fully synonymous with the previous one, as some non-ICU wards have the skills, equipment and trained manpower required to manage patients on noninvasive ventilation (NIV) [11, 12]. However, implementation of NIV outside the ICU can be envisaged only if these prerequisites are met.

Several scores have been proposed to predict the short-term outcomes of patients with COPD exacerbations, in order to facilitate and formalise orientation decisions [13–15]. Some are based exclusively on clinical criteria (*e.g.* age, number of clinical signs of severity,

 https://doi.org/10.1183/2312508X.10016516

Table 1. Criteria recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for referring patients to the hospital and admission to medical or respiratory ICUs

Decision	Criteria
Hospital assessment	Severe symptoms, such as sudden worsening of resting dyspnoea, increased respiratory rate, decreased oxygen saturation, confusion and drowsiness
	Acute respiratory failure
	Onset of new physical signs (*e.g.* cyanosis, peripheral oedema)
	Failure to respond to initial medical management
	Presence of serious comorbidities (*e.g.* heart failure or newly occurring arrhythmias)
	Insufficient home support
ICU admission	Severe dyspnoea that responds inadequately to initial emergency therapy
	Changes in mental status (confusion, lethargy, coma)
	Persistent or worsening hypoxaemia ($P_{a}O_2$ <5.3 kPa or 40 mmHg) and/or severe/worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and noninvasive ventilation
	Need for invasive mechanical ventilation
	Haemodynamic instability with need for vasopressors

Information from [2].

dyspnoea level at steady state, comorbidities) [15], while others also rely on biological data (blood eosinophil count) and/or chest autoradiography (consolidation) [13]. Additionally, some biomarkers have been tested for their prognostic value [16]. In general, the value of these prognostic rules is not sufficiently established to recommend their generalised use, so that the standard remains to assess patients using the criteria described in table 1. To be recommended, new prognostic scores would require external validation and, most importantly, prospective confirmation that their use decreases hospitalisations without increasing the risk of a poor outcome, as was determined for the Pneumonia Severity Index [17].

Pharmacological treatment of exacerbations

The cornerstone medications for COPD exacerbations are bronchodilators, antibiotics and systemic corticosteroids.

Bronchodilators

The main questions regarding bronchodilators deal with the choice of the pharmacological class to be used and the best mode of administration. The evidence regarding the comparative efficacy and tolerance of short-acting β_2-adrenergic and anticholinergic agents, alone or combined, does not provide clear clues to guide choices: comparative trials are not numerous and most were performed before the era of long-acting maintenance bronchodilator therapy, which makes it difficult to extrapolate their results to patients treated following the current standards for long-term therapy. In addition, systematic reviews were not able to conclude as to the superiority of one short-acting bronchodilator over another, or of their combination over either class used alone [18]. With that in mind, most guideline documents recommend the use of short-acting β_2-agonists with or without anticholinergic agents [2]. The inhalation route is preferred over intravenous use for β_2-agonists, extrapolating results from a landmark study in asthma [19]. Inhaled

short-acting bronchodilators can be administered using nebulisers or hand-held inhalation devices. Among these, dry powder inhalers require vigorous and deep inhalation, leading to a preference for metered-dose inhalers (MDIs) in the most severe cases, as they deliver the dose more effectively with slow inhalation [20]. Spacers can ease the use and efficacy of MDIs. Systematic reviews did not find an advantage of nebulisers over MDIs with or without spacers [21]. Therefore, the choice depends more on the setting and on practical considerations. Although some studies have suggested that an MDI plus spacer may be more cost-effective than a nebuliser [22], this finding is probably not universal, as nebulisation may actually be time-sparing for healthcare professionals.

Antibiotics

A recent systematic review found consistent effects of antibiotics on the risk of treatment failure in patients with severe COPD exacerbations hospitalised in the ICU or outside the ICU [23]. In the ICU, beneficial effects extended to mortality [23]. In outpatients, the evidence was less conclusive due to the lower quality of studies [23]. As a result, indications for antibiotics in COPD exacerbations outside the ICU remain an area of debate. Indeed, prediction of the bacterial *versus* viral aetiology of an exacerbation is difficult [24]. Purulence, and more specifically the green or yellow colour of sputum, is a rather simple clinical criterion with high sensitivity but low specificity [25]. In a nonrandomised study, a decision strategy based on this criterion decreased the use of antibiotics (*versus* systematic prescription irrespective of sputum colour), but this strategy was not compared with systematic antibiotic therapy in terms of patient outcomes [26]. In this study, serum CRP, but not procalcitonin (PCT), was associated with sputum purulence. However, data on the yield of CRP do not provide homogeneous results, probably because viral infections also induce increases in CRP levels [27]. Other studies have found that PCT may be of interest to reduce antibiotic prescriptions without any harm to patients, but the level of evidence is not sufficiently high to propose strong guidelines due to methodological limitations including small sample sizes [28]. In addition, sputum colour-based and PCT- or CRP-based strategies have not been compared directly, which would certainly be of major interest for clinical guidance. When an antibiotic treatment is decided, the recommended duration is 5–7 days [2]. Meta-analyses have suggested that second-line antimicrobial agents (*i.e.* amoxicillin/clavulanic acid, macrolides, second- or third-generation cephalosporins, and quinolones) are more effective than first-line agents (*i.e.* amoxicillin, ampicillin, pivampicillin, trimethoprim/sulfamethoxazole and doxycycline) for AEs of chronic bronchitis [29, 30], with limited differences in side-effect profiles. However, these analyses could not identify clinical or biological markers to guide the choice among these options. Thus, local patterns of resistance, costs, side-effect profiles and selective pressure need to be considered. Sputum samples should be taken for culture to search for resistant bacteria in patients with recurrent exacerbations, severe airflow limitation or requiring mechanical ventilation [2].

Corticosteroids

Importantly, the following considerations apply only to COPD without asthma. When these two diseases are associated or cannot be distinguished based on medical history (including lung function tests when available) and clinical presentation, oral corticosteroids should be used as for asthma exacerbations. The vast majority of available evidence on the role of systemic corticosteroids for AEs of COPD comes from hospital-based studies, which showed positive effects on the rate of treatment failures (relative reduction of ~50%, number needed to treat: nine), length of stay in the hospital (1 day spared), and speed of lung function and oxygenation improvement, but no difference in terms of mortality [31].

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These studies were performed in hospitalised patients or patients recruited in the emergency department, which makes it difficult to generalise their results to patients cared for in a purely outpatient setting. Some studies comparing intravenous with oral routes did not show significant differences, except in the risk of hyperglycaemia, which was higher with the intravenous route in one study [31]. In the specific subgroup of ICU patients requiring ventilatory support, conflicting data have been published [32, 33].

Importantly, systemic corticosteroids are associated with an increased risk of side-effects (number needed to harm: six). In addition, observational studies have suggested that, in the long term, there is an association between oral corticosteroid use and mortality or less beneficial effects of nutritional supplementation as part of pulmonary rehabilitation [34, 35]. Due to the nature of these studies, it is not possible to exclude biases such as occult differences between patient groups; moreover, the treatment of interest was low-dose maintenance therapy with oral corticosteroids, which has a different potential for side-effects when compared with short courses of these treatments. However, these results need to be kept in mind when trying to weight the risk/benefit ratio of oral corticosteroids for acute COPD exacerbations. As always, the final decision needs to be taken on an individual basis, especially considering comorbidity-related risk factors for side-effects and the frequency of exacerbations. With the aim of limiting the cumulative dose of systemic corticosteroids, it could be proposed to limit their use to patients exhibiting failure of initial treatment with bronchodilators with or without antibiotics (depending on sputum colour) at 48–72 h (figure 1), especially for patients with frequent exacerbations (in whom the cumulative dose would rapidly increase if these agents were used systematically). However, such a strategy has not been tested formally, leading most guideline documents to recommend more systematic use based on available studies [2]. Another strategy to limit the use of oral corticosteroids could be to refrain from prescribing them in patients with lower blood eosinophil counts, indicating a lower likelihood of benefit and a lower risk of relapse (despite a higher risk of poor short-term outcomes) [36–38]. However, the outcome of such a strategy remains to be further confirmed. Shortening the duration of systemic corticosteroid treatment is an obvious way of limiting the risk of side-effects, and current

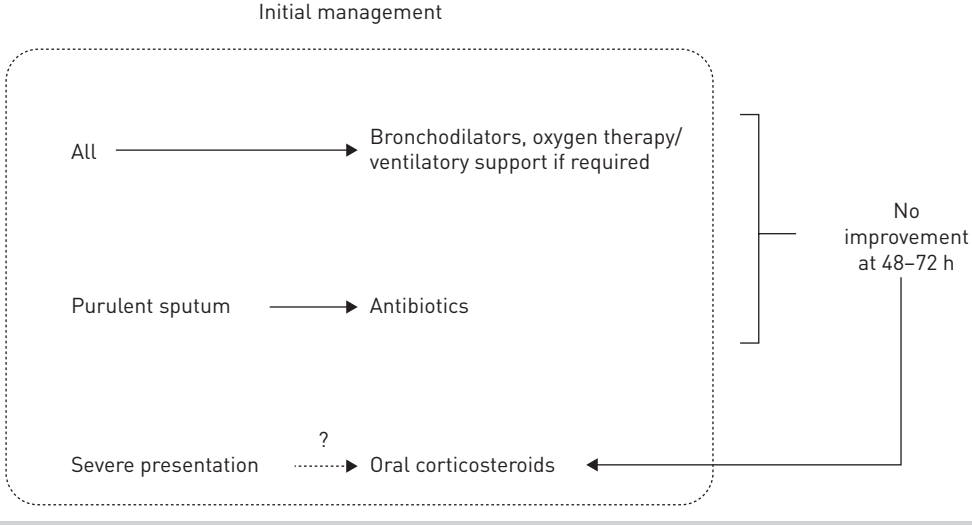

Figure 1. Proposed pharmacological management of acute COPD exacerbations.

recommendations based on available evidence [39, 40] plead for a 5-day duration [2]. Finally, some studies have suggested that inhaled corticosteroids (ICSs) could have similar effects to oral agents in some patients [41–43], but the evidence needs to be expanded.

Nonpharmacological components of care for exacerbations

Oxygen therapy and ventilatory support

High-concentration oxygen therapy leads to greater increases in P_{aCO_2} and greater risk of respiratory acidosis when compared with titrated oxygen treatment [44]. Thus, it is recommended to titrate oxygen therapy to maintain arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) between 88% and 92%, without omitting to check arterial blood gases for hypercapnia [2]. Titrated oxygen through nasal high-flow air cannulae could be of interest to reduce transcutaneous carbon dioxide tension (P_{tcCO_2}), although the clinical significance of the effect (−1.4 mmHg on average) is uncertain [45]. A P_{tcCO_2} decrease could be due to mechanical effects with increased tidal volume and end-expiratory lung volume relating to a continuous positive airway pressure effect [46]. Further prospective comparative studies are required to identify the best indications and conditions for this approach.

Table 2 summarises the indications for noninvasive and invasive mechanical ventilation, as proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [2]. When indicated, NIV has very high success rates (⩾80%), its most important effects being reductions in mortality, intubation rates, ventilator-associated pneumonia and length of hospital stay [47]. It can also be used as a weaning strategy for patients on invasive ventilatory support [48]. It is crucial to ensure that healthcare professionals involved in NIV implementation have the required knowledge, skills and experience. Patients should be

Table 2. Indications of noninvasive and invasive ventilatory support recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)

Ventilatory support	Indications
Noninvasive mechanical ventilation	At least one of the following: Respiratory acidosis (arterial pH ⩽7.35 and/or P_{aCO_2} ⩾6.0 kPa or 45 mmHg) Severe dyspnoea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen or retraction of the intercostal spaces Persistent hypoxaemia despite supplemental oxygen therapy
Invasive mechanical ventilation	Unable to tolerate NIV, or NIV failure Respiratory or cardiac arrest Diminished consciousness, psychomotor agitation inadequately controlled by sedation Massive aspiration or persistent vomiting Persistent inability to remove respiratory secretions Severe haemodynamic instability without response to fluids and vasoactive drugs Severe ventricular or supraventricular arrhythmias Life-threatening hypoxaemia in patients unable to tolerate NIV

NIV: noninvasive ventilation. Information from [2].

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closely monitored to avoid delayed intubation in case of NIV failure [49]. NIV should be accompanied by appropriate pharmacological treatment and physiotherapy whenever necessary to improve bronchial drainage [49].

Extracorporeal carbon dioxide removal has the potential to avoid intubation, facilitate extubation and reduce the length of invasive ventilation in hypercapnic respiratory failure due to COPD exacerbations. However, in the absence of RCTs and considering its side-effects (mostly bleeding), this approach should still be considered experimental [50].

Chest physiotherapy

Improving mucus clearance could help decrease airway resistance and increase airway defences. A variety of techniques have been evaluated, although in most cases the studies were small and did not focus on "hard" clinical end-points such as overall treatment failure rate or length of hospital stay [51]. A recent 6-month pragmatic open RCT in 526 hospitalised patients with COPD exacerbations and sputum production (327 with evaluable primary outcome data) did not show a significant benefit from manual chest physiotherapy (chest percussion, vibration and assisted coughing) added to active cycle of breathing techniques [52]. The interest in devices generating positive end-expiratory pressure, flutter effects and high-frequency chest wall oscillation needs to be explored further [53].

Care bundles

Care bundles can be defined as a set of evidence-based rules that should be systematically implemented. In the field of COPD exacerbations, care bundles have been developed for admission, hospital care and discharge [54–57]. The items of admission care bundles comprise the assessment (symptoms and history, S_{pO_2}, arterial blood gases, chest autoradiograph, specialist review), orientation and treatment (medications, oxygen therapy, ventilatory support). Many admission care bundles provide a time frame for actions to be taken within, for example 1 or 4 h. Discharge care bundles focus on smoking cessation aid, education and self-management plans, rehabilitation, inhaler technique assessment and follow-up appointments. Some bundles combine standards of care for admission, hospital care and discharge/follow-up. Overall, studies have shown beneficial effects of care bundles in terms of standards of care implementation, mortality, length of stay, risk of readmission and costs [54–57].

Early discharge

The rate of hospitalisation of patients visiting the emergency department can vary from one setting and healthcare system to another, but is often high [14]. However, not all hospitalised exacerbations are life-threatening, and hospitalisation is often prolonged due to insufficient resources at home. Therefore, several programmes of hospital-at-home or early supported discharge have been developed for implementation from the emergency department or following a shortened hospital stay. These programmes may be applicable to only a minority of admitted patients [58], but they do reduce length of stay without impairing patient outcomes, such as treatment failure or readmission rate [59]. Trends towards greater short-term improvements in health-related QoL have also been observed [60], as well as trends towards reduced mortality [59]. However, it must be noted that a recent meta-analysis found considerable heterogeneity between studies in terms of the structure of hospital-at-home/early supported discharge programmes, particularly regarding patient selection and level of support [59]. This makes it difficult to generalise the conclusions of these studies, and emphasises that local initiatives need to be evaluated appropriately.

Prevention of COPD exacerbations

As with acute-phase care, exacerbation prevention relies on both pharmacological and nonpharmacological interventions that exert complementary effects. Prevention can target the occurrence of these events and/or their risk of poor outcome. Virtually all clinical trials have categorised exacerbations pragmatically as mild (self-managed), moderate (requiring antibiotics and/or corticosteroids) or severe (hospitalised). Clearly, the two last categories are of greater clinical and societal relevance, while the significance and impact of mild events need to be explored further.

Pharmacological therapy for patients at risk of exacerbations

Several drug classes reduce exacerbation frequency. Among inhaled treatments, this effect has been demonstrated for long-acting bronchodilators (both long-acting β_2-agonists (LABAs) and anticholinergic agents such as long-acting muscarinic antagonists (LAMAs)) and ICSs, especially when combined with LABAs. Regarding oral treatments, macrolides, phosphodiesterase type 4 (PDE4) inhibitors and mucoactive antioxidants also have this potential, although in more specific populations.

Inhaled therapy: bronchodilators, ICSs and combinations

A beneficial effect on exacerbation frequency has been demonstrated for both LABAs and LAMAs [61, 62], although the underlying mechanisms are not well understood. In a meta-analysis of RCTs published before 2012, tiotropium was superior to LABAs for exacerbation prevention [63]. This was further confirmed 1 year later in a study of tiotropium *versus* indacaterol [64]. Although there have been some concerns on possible cardiac side-effects of bronchodilators, the currently available evidence is reassuring, providing these agents with a favourable risk/benefit ratio overall [65, 66]. However, it must be noted that all RCTs excluded patients with unstable cardiovascular disease, making it impossible to extrapolate the results to this specific population [67]. Reassuringly, recent observational studies did not identify specific safety signals [68]. However, more evidence is needed regarding combinations of LABAs and LAMAs [69, 70].

ICSs also prevent exacerbations, but expose patients to an increased risk of pneumonia [71]. Whether this side-effect is a class effect or differs among drugs has been an area of debate [72]. Overall, the risk of pneumonia needs to be taken into account when estimating the risk/benefit ratio of using ICSs in an individual patient [73, 74], even if pneumonia does not appear to be associated with an increased mortality risk. Other consequences of ICSs should be considered, falling into two categories: lung infections with tuberculous mycobacteria or NTM, or possibly *Aspergillus* spp. [75–77], and systemic effects including skin bruising, diabetes mellitus, osteoporosis and cataracts [78]. Among these, there is evidence from RCTs for skin bruising [79] and tuberculosis [76]. Importantly, the ability of ICSs to induce skin bruising demonstrates that these agents do circulate in sufficient amounts to induce clinically relevant systemic effects. Evidence of other infectious or systemic side-effects comes from observational studies. Another interesting consideration from a risk/benefit perspective is that ICSs and LABAs used as monotherapy appear to have similar efficacy on exacerbation rate [80].

Two types of combined inhaled treatments for COPD now exist: LABA+LAMA and LABA +ICS combinations. These were first compared with monotherapy, before recent studies

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compared them face to face. LABA+LAMA combinations have greater effects than LAMA alone on exacerbations in patients at risk [81]. A LABA+ICS combination has been compared with ICSs, LABAs and LAMAs alone, with superiority over LABAs and ICSs for exacerbation prevention [82]. Differences between LABA+ICS and LAMAs are less clear [83]. Conversely, a LABA+LAMA combination proved superior to a LABA+ICS combination in patients with a history of exacerbation and significant dyspnoea (modified Medical Research Council dyspnoea scale of $\geqslant$2) [84]. Triple combinations of LABA +LAMA+ICS are currently being developed and are more effective than LAMA alone or LABA+ICS at exacerbation prevention [85–87]. Whether these triple combinations are also superior to LABA+LAMA remains to be demonstrated, and is the topic of several ongoing trials (ClinicalTrials.gov numbers NCT02579850, NCT02164513 and NCT02465567).

Importantly, patients with features suggestive of associated asthma or of an "asthma component" (who enter into the asthma–COPD overlap category) always need to receive ICSs when maintenance therapy is indicated [88]. A higher blood eosinophil level could be another criterion for ICS prescription. Several observational studies have suggested that this biomarker is positively associated with exacerbation risk [89–91], although not all data are in agreement with this [92]. Additionally, *post hoc* analyses suggest that blood eosinophil levels predict the beneficial effects of ICSs on exacerbation frequency [93–96]. However, again not all studies provide concordant results in this area, probably due to differences in factors such as the study populations, and comparator or baseline/associated therapy [97, 98].

Last but not least, a major issue regarding inhaled therapy is that, to be effective, inhalers need to be used properly. Therefore, personalising device choice and checking technique are crucial [20], as misuse is associated with greater risk of exacerbations and poor disease control [99, 100].

Oral drugs: macrolides, PDE4 inhibitors, theophylline and mucoactive agents

A reduction in exacerbation rate has been shown with some macrolides (*i.e.* erythromycin and azithromycin) that have immunomodulatory and anti-inflammatory properties [101–104]. Whether these properties account for the preventative effect or whether they relate to antimicrobial and/or antiviral effects, modulation of bacterial virulence and biofilm formation, or modification of the local microbiota is not well understood [105]. The best indications of long-term macrolide preventative therapy are not clearly defined: the largest study was performed in rather heterogeneous patients included because they were on oxygen therapy or had received oral corticosteroids for exacerbations in the previous year, had gone to an emergency room or had been hospitalised for an AE of COPD [101]. The best target subgroup according to a *post hoc* analysis comprised older patients and milder levels of airflow limitation [106], but this needs to be explored further. Another study focused on patients with three or more exacerbations in the previous year, most of whom were on maximal inhaled therapy [102]. The optimal dosage and duration of azithromycin therapy is not well defined: one study used 500 mg three times a week [102] and another used 250 mg daily [101], and no study duration exceeded 1 year. The risk/benefit assessment needs to account for the risks related to prolonged QTc interval, hearing impairment, incident resistant bacteria, changes in the microbiota and selective pressure on NTM. Therefore, it seems mandatory to check the ECG, sputum (for mycobacteria) and hearing before initiating azithromycin [107].

PDE4 inhibitors also prevent exacerbations through anti-inflammatory effects mediated by inhibition of the breakdown of intracellular cyclic AMP. Following *post hoc* analysis of

earlier RCTs and further prospective confirmation, the target population is defined as patients with a history of exacerbations, severe airflow obstruction and chronic bronchitis [108, 109]. The beneficial effects on exacerbation frequency have been demonstrated in patients receiving long-acting bronchodilators or ICS+LABA fixed-dose combinations [108, 110]. Side-effects are relatively frequent, including gastrointestinal symptoms and limited weight loss (mostly relating to decreased fat mass).

At therapeutic doses, theophylline does prevent COPD exacerbations [111]. However, the use of this drug is limited by potential side-effects and a narrow therapeutic index. However, theophylline also inhibits phosphoinositide 3-kinase and thereby increases the activity of histone deacetylase 2, a cofactor for the anti-inflammatory effects of ICSs. It has thus been hypothesised that theophylline could revert the decrease in corticosteroid sensitivity observed in airway inflammatory cells from COPD patients [112, 113]. However, a recent RCT contradicted the clinical relevance of this hypothesis and did not find any supplemental effect on airway inflammation and exacerbation rate when low-dose theophylline was added to ICS [114].

Mucoactive agents with antioxidant properties have been shown to decrease the risk of exacerbations. However, this effect was found only in patients who did not receive ICS, despite having an indication for this drug class [115], or in Asian populations [116]. Therefore, in most guidelines, mucoactive agents are not recommended for widespread use [2], although their prescription could be considered in patients who still suffer from exacerbations despite all other treatment options.

Vaccines

The purpose of pneumococcal vaccination includes reducing the risk of lower respiratory tract infections requiring hospitalisation, community-acquired pneumonia and COPD exacerbations. Polysaccharide vaccines reduce the risk of all community-acquired pneumonia and COPD exacerbations, but there is no evidence of pneumococcal pneumonia prevention. Conversely, the conjugated vaccine prevents vaccine-type bacteraemic and nonbacteraemic pneumonia, but not community-acquired pneumonia from any cause [117–119]. The conjugated vaccine has greater immunogenicity but covers fewer serotypes, leading to proposals of the combination of these two options (conjugated vaccine, followed $\geqslant$8 weeks later by polysacharide vaccine) [120]. Influenza vaccination also reduces exacerbation risk [121], and the two types of vaccine administered together could have additive effects during the first year following vaccination, compared with influenza vaccination alone [122].

Nonpharmacological approaches to decrease the risk and impact of exacerbations

Smoking cessation

Smoking cessation is obviously the most important measure in patients with COPD (as in all smokers in general). Therefore, it is the duty of all healthcare professionals involved in the care of these patients to provide them with aids to help smoking cessation, and to give them access to smoking cessation programmes. Whether smoking cessation is associated with decreased exacerbation risk is difficult to establish, as only a minority of smokers involved in smoking cessation therapeutic trials actually stop smoking durably, and the natural history of smoking habits is often characterised by phases of success and relapse in

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dependent patients. However, some studies found a decrease in the occurrence of lower respiratory tract infections in patients who managed to stop smoking [123].

Education, self-management, action plans, integrated care and telemedicine

The goal of education in COPD patients is to increase not only their knowledge of the disease and treatments, but also smoking cessation rate, healthy nutrition, adherence to treatment, correct use of inhaler devices, early recognition and appropriate care for exacerbations, and daily physical activity. In other words, the most important target of education is not knowledge but behaviours. Several RCTs showed that self-management interventions based on action plans, education and support were able to decrease the risk of hospitalisation for COPD exacerbations and related healthcare costs, with long-lasting effects (up to 2 years). Concomitant effects on health-related QoL and dyspnoea have been found [124–126], with improvements in QoL being observed, in particular with self-management interventions that include an education component [127]. In addition, adherence to written action plans is associated with shortened recovery time from exacerbations, probably due to earlier treatment [128]. Importantly, action plans with brief patient education (one session), but without a comprehensive self-management programme, reduce in-hospital healthcare utilisation and increase appropriate treatment of COPD exacerbations [129].

Integrated care or integrated disease management has been defined in many ways. It corresponds to a process comprising several coordinated interventions implemented through a structured multidisciplinary approach, aiming to improve patient outcomes while containing costs [130]. Self-management is promoted as part of integrated care. Although a meta-analysis concluded that integrated disease management could improve QoL and exercise tolerance while reducing hospital admissions and number of hospital days [130], some studies found negative results in terms of both clinical outcomes and cost-effectiveness that were not explained by variations in the intensity of the programme's implementation [131, 132]. This discrepancy might be explained by the heterogeneity of integrated care programmes in terms of recruited populations and components of care. The same comment actually applies to self-management interventions, making it difficult to identify the most effective components of these interventions packages, although those that contain exercise seem the most effective [133].

There is increasing curiosity towards the use of modern technology to empower patients. A recent review of smartphone interventions suggested a potential to reduce COPD exacerbations, although the studies varied in terms of type of intervention, data collection from the participants and feedback strategy [134]. As a result, heterogeneity precluded drawing firm conclusions. Telemedicine can also rely on telemonitoring with feedback to the patient, their healthcare providers or a platform with "intermediate" healthcare professionals, and/or on educational or supportive interventions aimed at improving behaviours. A recent review of various telemedical interventions concluded that the available evidence did not allow a conclusion regarding their effects on risk of hospitalisations, exacerbations, visits to the emergency department or healthcare costs [135]. Again, the heterogeneity of interventions makes it difficult to get a consistent picture of what can be expected from these approaches, although they definitely have great potential, provided that proposed interventions are acceptable by patients, healthcare professionals and society. Indeed, a comprehensive smartphone/tablet-based bidirectional programme relying on a computer algorithm and on nurses and doctors proved effective in decreasing the frequency and severity of exacerbation symptoms and improving the detection and treatment of exacerbations [136, 137].

Finally, coaching is gaining interest in the COPD field, as in other areas that go far beyond health. Health coaching, as self-management interventions and integrated care/complex interventions, requires "a process of iterative interactions between patients and/or relatives and one to multiple healthcare providers with the goals of motivating, engaging, and supporting the patients to better manage their disease and adopt healthy behaviours" [138]. It relies particularly on motivational interviewing and is patient centred, while using "classical" self-management tools, such as action plans. Beneficial effects on the risk of readmission have been reported in COPD patients hospitalised for an exacerbation [139].

Pulmonary rehabilitation

Rehabilitation provides integrated and structured multidisciplinary programmes, focusing especially on exercise and education. Strikingly, a Cochrane collaboration publication concluded in 2015 that RCTs comparing rehabilitation with usual care were no longer needed, considering the considerable body of evidence demonstrating the positive effects of rehabilitation not only on physiological exercise variables, but also on general (fatigue) and respiratory (dyspnoea) symptoms, emotional function, coping strategies and sense of control, and QoL [140]. Interestingly, this systematic review suggested, although with moderate confidence, that hospital-based programmes could be more effective than those implemented in the community setting (the difference was observed with the Chronic Respiratory Questionnaire, but with not the Saint George's Respiratory Questionnaire) [140]. It also suggested, again with moderate confidence, that simple exercise-based interventions could be as effective as more complex interventions with comprehensive education programmes. These observations underline the remaining need to explore the best modalities of rehabilitation implementation from both a clinical and a medico-economic perspective.

Along this line, one specific question is whether rehabilitation following an exacerbation is useful or detrimental, as recently explored in an RCT [141]. The conclusion of a dedicated systematic review was that, while health-related QoL and exercise capacity improve after post-exacerbation rehabilitation, data on readmissions and mortality are contradictory, which is probably due to heterogeneity in terms of rehabilitation conduct, and warrants further investigation [142].

Noninvasive ventilation

Following several years of debate and contradictory data on the outcome of long-term home NIV in COPD patients, a recent trial in patients with persistent hypercapnia (P_{aCO_2} >53 mmHg) 2–4 weeks after resolution of respiratory acidaemia found that this strategy increased time to readmission or death and decreased exacerbation rate [143]. This confirmed the results of an earlier trial finding beneficial effects of long-term NIV on survival, in patients with similar levels of hypercapnia than in the abovementioned study, and levels of inspiratory pressure targeted to reduce baseline P_{aCO_2} by at least 20% or to achieve P_{aCO_2} values <48.1 mmHg [144].

Lung volume reduction

In the National Emphysema Treatment Trial (NETT), a decrease in exacerbation rate of 30% and a concomitant increase in time to first exacerbation were observed in patients in the active arm of the trial [145]. Interestingly, this benefit increased in patients with increasing FEV1 improvement, suggesting that the improvement in lung mechanics was the mechanism involved [145]. When transposing these results in clinical practice, other results of NETT in terms of survival and QoL need to be kept in mind: a survival advantage was

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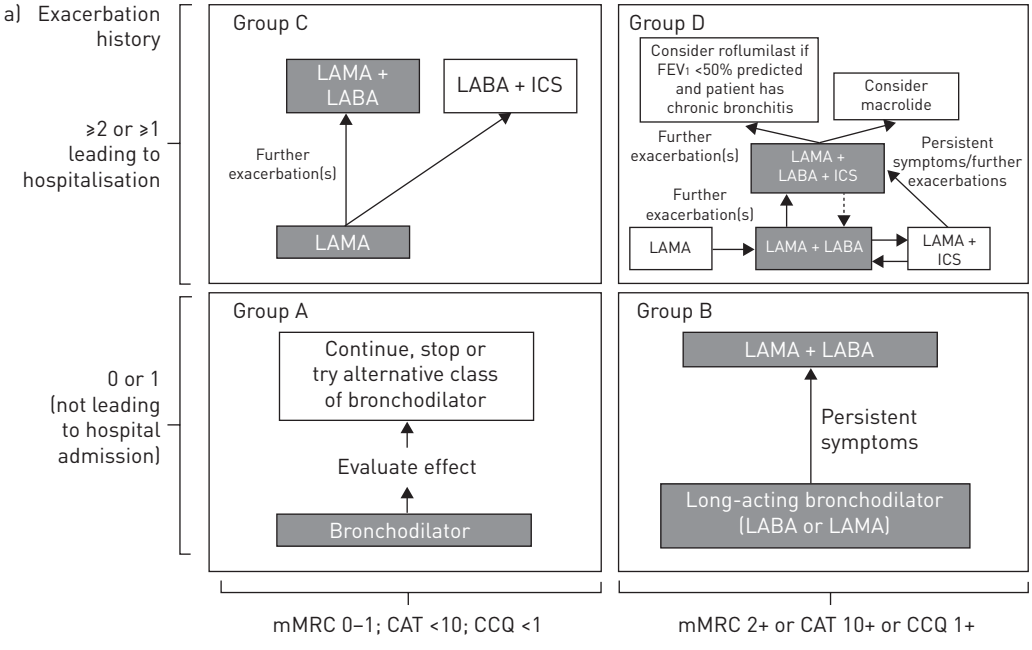
found only in patients with heterogeneous emphysema and low exercise capacity, but with a not too severe impairment in FEV_1 and diffusion capacity of the lung for carbon dioxide (D_{LCO}) [146, 147]. Conversely, a survival disadvantage was found in patients with non-upper-lobe predominance and high baseline exercise capacity, and when FEV_1 or D_{LCO} was <20% predicted. In all categories except these last ones, a QoL improvement was observed.

Recommendations

Considering the abovementioned evidence, several guidelines, recommendations or (pro) positions have been produced by various bodies or experts. Figure 2 shows the 2017 recommendations by GOLD, based on the level of symptoms and history of exacerbations. Figure 3 corresponds to an alternative expert proposition published recently, showing the trend towards earlier phenotyping to target pharmacological treatment choices in a more personalised way [148]. Results of studies on the yield of biomarkers, the comparative

a)



b)

Patient group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacological treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B–D	Smoking cessation (can include pharmacological treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

Figure 2. Global Initiative for Chronic Obstructive Lung Disease (GOLD) propositions for COPD a) pharmacological and b) nonpharmacological treatment. LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid; mMRC: modified Medical Research Council dyspnoea scale; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire. Reproduced and modified from [2] with permission.

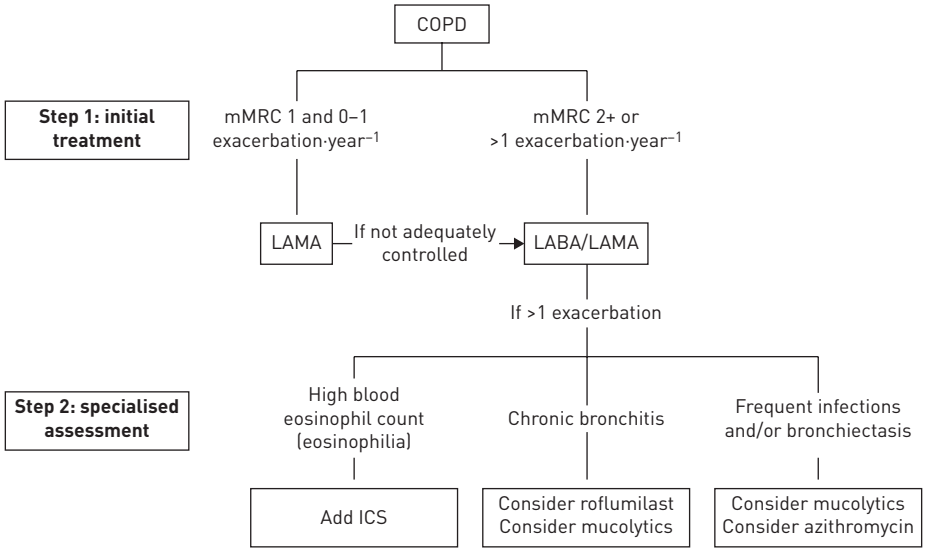


Figure 3. An alternative algorithm for COPD pharmacological management. mMRC: modified Medical Research Council dyspnoea scale; LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroids. Reproduced and modified from [148] with permission.

efficacy of pharmacological treatment combinations and the most effective components of integrated disease management are needed to refine future recommendations.

Conclusion

Although some issues remain unsolved, there is a large body of published literature on the treatment and prevention of exacerbations in patients with COPD. Many guidelines, recommendations and propositions have been produced in this area, which aim to improve the short- and long-term outcomes of patients. For these to be effective from a clinical perspective and efficient from a medico-economic perspective, they first need to be implemented properly. However, many surveys and audits have found much room for improvement in clinical practice [149, 150]. Thus, future efforts should be directed not only at producing new evidence answering remaining questions and new treatment strategies addressing unmet needs, but also at improving the implementation of recommendations in real-life care.

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Disclosures: N. Roche reports receiving grants and personal fees from Boehringer Ingelheim, Novartis and Pfizer, and personal fees from Teva, GSK, AstraZeneca, Chiesi, Mundipharma, Cipla, Sanofi, Sandoz, 3M and Zambon, outside the submitted work.

 https://doi.org/10.1183/2312508X.10016516

Chapter 12

Cystic fibrosis: treatment and prevention of pulmonary exacerbations

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Pulmonary exacerbations are frequent and clinically important events in the natural history of CF. The frequency of pulmonary exacerbations is associated with poor clinical outcomes. Preventing pulmonary exacerbations is a high priority in delivering optimal care for people with CF. A number of therapies have been shown to reduce pulmonary exacerbations in clinical trials, and these should be used in a targeted way in individual patients. When pulmonary exacerbations occur, treatment should be commenced promptly, and for each event, people with CF and their multidisciplinary team should consider the optimal treatment regime with new antibiotics combined with augmentation of regular therapies.

Cite as: Elborn JS. Cystic fibrosis: treatment and prevention of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 167–180 [https://doi.org/10.1183/2312508X.10016616].

Pulmonary exacerbations in people with CF are catastrophic events that occur intermittently and are associated with increased respiratory and systemic symptoms, increased inflammation in the lung and loss of lung function [1–6]. Frequent exacerbations are associated with reduced survival and QoL, and are associated with a more rapid decline in lung function [3, 7, 8]. Pulmonary exacerbations occur in ∼50% of adults and ∼25% of children each year, and increase in frequency with disease severity [9]. Preventing pulmonary exacerbations and treating them effectively is likely to have a major impact on long-term outcomes and should be a primary focus of CF care delivery [2]. A number of treatments that have reduced time to next exacerbation or the frequency of exacerbations in clinical trials are associated with reduced lung function decline or better survival in registry studies [2, 10, 11]. A number of registry studies have also demonstrated that greater use of intravenous antibiotics in centres is associated with a better mean FEV_1, suggesting that an interventionist approach to exacerbations preserves lung function [12, 13].

Pulmonary exacerbations are generally considered to be driven by bacterial, viral or fungal infection. A disturbance of the homeostatic balance in the airways of patients with chronic

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

infection in some way precipitates an amplified inflammatory response (figure 1) [4]. This may be due to external factors, such as new viral or bacterial infection, inhaled pollutants or changes in the host/bacterial equilibrium in the niche of the airway [14]. However, the biology and dynamics of the dysbiosis that occurs during exacerbations is not well understood. It is likely that the chronically infected airway is a complex system and that a combination of small changes in external factors, microbiota and host response in some circumstances results in the precipitation of an exacerbation event [2, 15]. Further research to understand the mechanisms involved in exacerbations should identify further targets for intervention. This is likely to require a systems biology approach.

In this chapter, the current treatment and prevention of pulmonary exacerbations will be discussed. Specific, difficult and controversial questions will be posed and practical comments offered based on the available literature and current practice. It is not the purpose, nor is it possible, in this short chapter to provide a comprehensive guideline to the treatment of exacerbations or their prevention. The questions posed are those facing practising physicians daily, particularly those providing care for older children and adults with CF who have chronic infection with *Pseudomonas aeruginosa*. Treating exacerbations takes up a considerable proportion of care delivery in older age groups and has an associated high cost [16]. Further research in this area to improve the efficacy of exacerbation treatment is important and is a high priority, as prevention and efficient treatment of exacerbations are likely to result in improved outcomes.

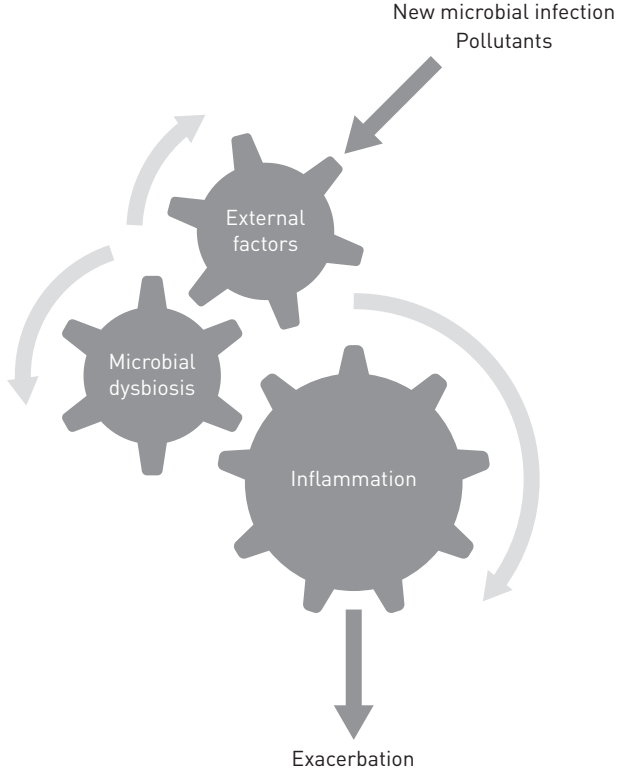

Figure 1. Schematic of infection and inflammation.

 https://doi.org/10.1183/2312508X.10016616

Treatment

Pulmonary exacerbations are generally treated with antibiotics, usually given systemically; in the case of people with CF who have chronic *Pseudomonas* infection, these are frequently administered *i.v.* [14, 17, 18]. Failure to treat exacerbations with antibiotics is associated with poor short- and long-term outcomes [13, 19]. The choice of antibiotic is based on prior knowledge of the patient's sputum microbiology [14, 19]. Patients who have chronic infection with *P. aeruginosa* and an exacerbation event are usually given two *i.v.* antibiotics from different classes [20, 21]. Most frequently, this is a combination of an aminoglycoside, such as tobramycin, and a β-lactam-based antibiotic with antipseudomonal activity, such as tazobactam, ceftazidime or meropenem. The duration of treatment is usually 14 days [22]. The evidence base for this approach is weak, and these regimes have developed through clinical observation, custom and practice. A similar approach is taken in individuals who have other nonfermenting, Gram-negative chronic infections [23].

In contrast, for exacerbations in patients who do not have chronic *P. aeruginosa* or another Gram-negative infection and where the primary organism is thought to be *Staphylococcus aureus*, *Haemophilus influenzae* or *Moraxella catarrhalis*, single-agent antibiotic therapy is used, again generally for 14 days. In patients with chronic infection with fungi or NTM as the dominant pathogen, the choice of specific antimicrobial agent and the length of treatment are more problematic, and there is considerable variation in practice [24]. The choice of antibiotic in this group is often helped by discussion with a microbiologist or infectious disease specialist.

Chronic therapies are usually augmented during these occasions, and patients are encouraged to increase the frequency of airway clearance treatments, including the use of mucoactive drugs [25]. In many of these events, there is associated weight loss due to anorexia and hypermetabolism, and increased energy intake is recommended to counteract this [26]. Additional therapies, such as corticosteroids, are frequently added to the antibiotic treatment. However, there is wide variation of practice in these interventions among centres, indicating uncertainty in the value of some of these treatments [27, 28].

Recently, several observational studies have shown that, in ∼30% of exacerbations, there is a failure to recover lung function to baseline or there is a further exacerbation within a short time period [29–32]. These results emphasise the propensity of these events to cause significant lung injury. It is not entirely clear why there is a failure to recover from an exacerbation. There is an association with raised CRP in several studies, indicating that amplified inflammatory responses in the airways are likely to be partly responsible [30, 33]. There are no evidenced-based strategies for further intervention in exacerbations where there is a failure to return to baseline FEV1 or resolve symptoms, or where there is a persistently elevated CRP. In these circumstances, antibiotics are often changed or prolonged, oral corticosteroids started, or other adjustments made in airway clearance and mucoactive therapies [25, 34]. However, there is little evidence from trials to justify any of these changes or new interventions.

The recommended practices around antimicrobial selection, dose, duration and route of administration have not been studied in large, appropriately designed clinical trials [1, 35]. Many of the practices were established in an era of empirical medicine. Most exacerbations do resolve following antibiotic treatment, so it is practically and unethically challenging to test alternative approaches, agents or duration of treatment [36, 37]. However, to improve outcomes in this context will require new methodologies to personalise exacerbation

treatments and ensure that patients receive the right antibiotics, in the right place, at the right dose and for the appropriate length of time. We also must determine what appropriate supportive therapy is helpful and consider whether adjuvant therapies that would increase antimicrobial activity or modulate information will be of benefit [38]. It may not be possible to determine the best approach for an individual patient from conventional clinical trials. Novel trial designs should be considered, as well as the application of artificial intelligence-based data analytics that take a Bayesian approach to data to help understand the likelihood of interventions succeeding in individual patients.

What factors should be considered in choosing *i.v.* antibiotics?

The choice of antibiotics to treat pulmonary exacerbations in CF is largely empirical. In initiating antibiotic treatment for exacerbation symptoms, identification of the pathogen and antimicrobial sensitivity testing information are not available in real time. This means that antibiotic decisions are made based on previous tests that predate the exacerbation event by weeks or months. For exacerbations associated with *S. aureus*, *H. influenzae* or *M. catarrhalis*, single-agent therapy based on previous antimicrobial sensitivities is a logical approach [39]. For exacerbations in patients with MRSA infection, dual-agent treatment may be preferable [40].

In patients with chronic *P. aeruginosa* infection, choosing antibiotics based on antimicrobial sensitivity testing does not result in better outcomes compared with an empirical choice [41–43]. This is very different to the principles in managing Gram-negative infection in acute sepsis. The reasons for this difference in chronic infection are multifactorial. In sputum microbiology in CF, multiple different resistant phenotypes are observed, and this makes interpretation difficult [44]. In addition, *P. aeruginosa* exists in both biofilm and planktonic forms *in vivo* [45]. These can have strikingly different antimicrobial sensitivities, and these and other micro-environmental factors including the complexities of microbiological communities are not reflected in current methods to determine antimicrobial sensitivity [46]. There are no robust clinical trials to suggest that any particular antibiotic or combination has advantages in treating pulmonary exacerbations in patients with *P. aeruginosa* infection [47]. The most common combination is an aminoglycoside (usually tobramycin) and a β-lactam-based antipseudomonal agent, such as ceftazidime, tazobactam, meropenem, temocillin or aztreonam; colistin can be substituted for tobramycin [37]. Other agents such as fosfomycin, cotrimoxazole and chloramphenicol may also have a role, but there are no controlled or comparative studies to assist in deciding when to introduce them. The decision about which combination to choose is usually based on previous responses by the patient, including their ability to tolerate particular drugs because of allergy or previous toxicity. For the treatment of NTM, nonfermenting Gram-negative bacteria other than *P. aeruginosa* and fungal infection, the choice of antimicrobial is based on expert opinion, a general understanding of probable antibiotic sensitivity and extrapolation from use in other diseases [23, 24].

What are the optimal route, dose, frequency and duration of delivery?

There is strikingly little evidence on which to base decisions around any of these questions. Most antipseudomonal antibiotics must be delivered *i.v.* There is debate as to whether *i.v.* extended-spectrum β-lactam antibiotics should be delivered by bolus or infusion, with some evidence in very small studies that there may be some advantage in infusion administration [48, 49]. In general, for extended-spectrum β-lactam antibiotics, there is a

 https://doi.org/10.1183/2312508X.10016616

paucity of pharmacokinetic/pharmacodynamic data to confirm that the widely used three times daily regimes are optimal. These studies are difficult, as there is considerable variation in antibiotic penetration into the lung and sputum [50]. Tobramycin is the aminoglycoside of choice, as it is associated with less toxicity compared with other aminoglycosides [51]. There is more clinical evidence for *i.v.* tobramycin use in CF. It should be administered in a single daily dose, as this is of equal efficacy and probably safer than multiple daily dosing [52, 53]. Most antibiotic courses for exacerbations are given for 14 days, although this may be shortened if patients are responding well in terms of symptoms and FEV_1, or prolonged if there is a lack of clinical response. However, there is little evidence of efficacy for either of the strategies, and this is being explored in an innovative adaptive design study called STOP (Standardized treatment of pulmonary exacerbations) [54]. For treatment of NTM, nonfermenting Gram-negative bacteria other than *P. aeruginosa* and fungal infection, the route doses and frequency are determined either by expert opinion or by extrapolation from use in other diseases [23, 24].

Nebulised antibiotics are not generally recommended for the treatment of pulmonary exacerbations, and in many centres it has been usual practice to stop inhaled antibiotics during a pulmonary exacerbation. The increasing prevalence of impaired renal function makes the alternative of inhaled tobramycin an attractive option to *i.v.* tobramycin in patients with renal damage. However, the evidence base for this is weak. Also, there is a reasonable logic in continuing inhaled antibiotics when additional *i.v.* antibiotics are being used to treat an exacerbation. Stopping an effective therapy during a pulmonary exacerbation lacks logic, and there is no evidence to suggest it is necessary. Care should be exercised if combining inhaled and *i.v.* tobramycin, as toxic concentrations could occur.

What should be monitored in patients and how often?

The main aims of treating an exacerbation in CF are to improve symptoms, increase FEV_1, and reduce local and systemic inflammation [35]. Measurements of symptom scores generally improve, although there are no validated tools to indicate how to use symptoms in a systematic way. FEV_1 is a useful objective measurement to monitor improvement [55]. Some centres monitor sputum volume or weight, but this has not been demonstrated to be of value in decision making [56]. Most of the FEV_1 improvement occurs in the first 7 days of a 14-day course [26]. Measurements of FEV_1 at around days 7 and 14 are helpful, although this seems to be variable among centres. Measurements of CRP and white blood cell count (neutrophils) are also of some value. A raised CRP at the beginning of an exacerbation or at the end is associated with failure to return to baseline [30]. CRP is usefully measured at the start and on days 7 and 14 of an exacerbation. Failure to improve symptoms or FEV_1, or to reduce CRP, should be a prompt to consider the current diagnosis and treatment. Aminoglycoside levels should be monitored in appropriate patients, primarily to ensure safety [37, 53]. Monitoring of other drug levels is currently not widely practised. Nutritional and metabolic monitoring is also important, as exacerbations can increase insulin resistance and precipitate or worsen CF-related diabetes [2].

Are *i.v.* antibiotics administered at home equivalent to an admission to hospital for *i.v.* therapy?

I.v. antibiotic therapy for pulmonary exacerbations can be delivered in a hospital or in the home setting [57–59]. Admission to hospital facilitates supportive strategies, particularly

optimising airway clearance, nutritional support and psychological input as appropriate. It provides a supportive context for patients to rest and have antibiotics delivered by the CF team. Some patients and parents prefer exacerbation therapy with *i.v.* antibiotics to be undertaken at home for a range of reasons, and in some healthcare systems home treatment is preferred. Some studies have suggested that home *i.v.* treatment for pulmonary exacerbations in CF is less effective, but there are no definitive data on this [59]. Each event should be considered on its merits based on infrastructure, severity and individual patients' priorities. Regardless of the location of treatment, the opportunity should be taken to review current preventative treatment, adherence to therapy and possible precipitating factors in the current exacerbation episode.

What are the best oral antibiotic therapy options?

Oral antibiotic therapy is routinely used in the treatment of exacerbations associated with *S. aureus*, *H. influenzae* and other organisms for which effective oral antibiotics are available. In exacerbations with severe symptoms, particularly if there is respiratory decompensation or systemic inflammation, *i.v.* antibiotics may be more effective. These events, although usually less severe than in people with Gram-negative infection, are associated with a negative impact on important outcomes, such as FEV_1 [60, 61]. For exacerbations associated with *P. aeruginosa* infection, oral ciprofloxacin may be a helpful alternative to *i.v.* antibiotics. Other antibiotics, such as cotrimoxazole, tetracyclines and chloramphenicol, have some activity against *Pseudomonas* spp. and may also be useful.

Is there a role for anti-inflammatory therapy?

The addition of an anti-inflammatory therapy to antibiotics to treat pulmonary exacerbations is an attractive proposition [62]. However, there is little evidence that the addition of corticosteroid therapy is of value in this context. Pulmonary exacerbations caused by allergic bronchopulmonary aspergillosis may benefit from corticosteroids, but there is little to support their routine use in exacerbations. Several new drugs are being developed with anti-inflammatory activity, and these may be useful in preventing exacerbations and also in treating exacerbations by increasing the dose temporarily [63, 64]. As these programmes develop, it will be interesting to see how anti-inflammatory treatment might be tailored around exacerbations.

What adjunctive therapies should be adjusted?

There is little strong evidence in this area. Physiological correction of hypoxia and hypercapnia are important in managing exacerbations in people with severe disease. This may require oxygen therapy and ventilatory support. Increasing airway clearance to match sputum production and the use of positive pressure may be helpful. Hypertonic saline may be useful as a new therapy, or the frequency of administration increased during the exacerbation [65]. There is little evidence that increasing the dose of dornase alfa (recombinant human DNase I) is a helpful intervention. Nutritional support with increased caloric intake, if possible, is important. All individuals having an exacerbation should have this area directly assessed by a nutritionist. Pulmonary exacerbations are major negative events for people with CF, and additional psychological support should be offered to all patients.

 https://doi.org/10.1183/2312508X.10016616

Prevention

The priority in the treatment of people with CF throughout their lifespan is the prevention of lung injury and impairment of pulmonary function. Operationally, this can be delivered by focusing care pathways on prevention of pulmonary exacerbations. Optimising nutrition and diabetes control, and prevention of chronic infection by interventions to eradicate Gram-negative and other bacteria, are important in prevention.

The primary aims in developing treatment plans for individuals with CF who have chronic infection should be to ensure that exacerbations are as infrequent as possible, to optimise QoL, and to maintain or improve spirometric measures of lung function. An optimally treated child or young adult should have no exacerbations each year, while the aim for those with more advanced disease should be to have no more than one exacerbation per year, as lung function decline is significantly greater and survival worse in people who have two or more pulmonary exacerbations per year. Treatments that reduce exacerbations often have other beneficial effects on well-being and improve lung function [66–68]. For example, weight gain is associated with a number of therapies that reduce exacerbations [67, 68].

Most therapies used to prevent exacerbations improve FEV1 by 5–10% and improve QoL scores (Cystic Fibrosis Questionnaire Respiratory Domain). These have mostly been trialled as additional therapy to the standard of care at that time. Many patients with CF will be undergoing several of these treatments, but it is unclear in what order they should be considered, whether they have additive benefit, and whether and how stopping a specific treatment might be managed. Polypharmacy is common practice in CF care, and this leads to an enormous burden of treatment [69]. Tailoring preventative therapies to individual patients could provide a way of rationalising this treatment burden. However, there are few studies that compare treatments within each class or between classes to inform this conversation with patients.

A reduction in the time to next exacerbation and the frequency of pulmonary exacerbations are important end-points in clinical trials for new therapies in people with CF. In some studies, pulmonary exacerbations have been the primary end-point, although more usually FEV1 has been the primary end-point, but as the decline in FEV1 is attenuated and the frequency of pulmonary exacerbations is reduced, using these as end-points in clinical trials is more difficult.

When should therapies to prevent exacerbations be commenced?

There are no studies that help in deciding when to start long-term therapies to prevent exacerbations. Mucoactive therapies are often started as general prophylaxis in early life, and there is some supporting evidence for dornase alfa [70], but not for hypertonic saline [71], in infants. This makes sense, as airway inflammation and injury can be detected in the first 3 years of life in a substantial number of children, and improving mucociliary clearance is likely to be beneficial. In general, antibiotics are started later in the disease progression when chronic infection with *P. aeruginosa* has been established [72]. CF transmembrane conductance regulator (CFTR) modulators such as ivacaftor and lumacaftor/ivacaftor reduce exacerbations and are indicated for this. In general, these treatments should be started as early as possible according to the label, although there are limited efficacy data in young children [73].

Which mucoactive therapies prevent exacerbations?

Airway clearance has been used as a treatment for all people with CF at all times in their lives [25]. This approach has recently been questioned in the newly diagnosed infant and in all children and adults who have little or no sputum production. It is not clear whether regular airway clearance prevents exacerbations, although in one of the few RCTs in this area an increase in pulmonary exacerbations was observed with vibrating vest-based therapy compared with an active cycle of breathing [25]. It is unlikely that future clinical trials will be undertaken to study this. Based on current knowledge in this area, airway clearance techniques should be individualised for each person and reviewed regularly, and the techniques adjusted or changed according to individual preference and disease progression [25]. Table 1 summarises the available mucoactive therapies that reduce pulmonary exacerbations.

There is a rationale for initiating hypertonic saline and dornase alfa in infancy, although neither has a specific licence for this. It is not clear whether there are differences in efficacy or whether there is an additive effect of using both. Overall, the trials favour dornase alfa, but both may be considered in the under-fives [80].

Inhaled mannitol reduces pulmonary exacerbations in adults and children, although the effect size appears to be less than for dornase alfa [79, 81]. However, these two therapies have not been directly compared.

Which antibiotic therapies reduce exacerbations?

In the UK, oral flucloxacillin prophylaxis has been used for many years from the time of diagnosis to prevent *S. aureus* infection [82]. This practice is based on some short-term and underpowered clinical trials [83, 84]. There was weak evidence that this may reduce exacerbations in the first 2 years in an old study when the standard of care was very different [84]. This approach is now being subjected to an RCT, as there are concerns that antibiotic therapy in infants may predispose to *P. aeruginosa* infection [85]. Further use of this approach should await the results of the current trial.

Table 1. Effects of mucoactive therapies that reduce pulmonary exacerbations

Treatment	Exacerbations	QoL	FEV_1	Other effects
Hypertonic saline	Decreased 50%	Increased	Increased 4%	
Dornase alfa	Decreased 20%	Increased	Increased 5–7%	Weight gain
Mannitol	NS[#]	NS	Increased 2–3%	Cough

There are no systematic data on the effect of airway clearance on any of these outcomes. NS: no significant change. [#]: mannitol did not reduce exacerbations significantly in two independent pivotal trials [74, 75], but did show a 29% reduction in a pooled analysis [76]; however, the 95% CI was 2–49%, making these data hard to interpret. Other studies agree with these results [77, 78]. In a further recent study in children, a reduction in exacerbations was observed, but not as a primary outcome measure, so it is difficult to estimate the effect size, as this was reported in the adverse events [79]. Information from [25, 70–81].

 https://doi.org/10.1183/2312508X.10016616

Table 2 summarises the current antibiotic therapies that reduce pulmonary exacerbations. Inhaled antibiotic therapies, particularly for individuals chronically infected with *P. aeruginosa*, have been an important contributor to improved outcomes in people with CF. A range of inhaled antibiotics is available. Inhaled tobramycin and aztreonam have strong clinical trial data demonstrating their benefit compared with placebo [35, 86]. Colistin as a dry powder or nebuliser solution does not have placebo comparisons, and the most recently approved inhaled antibiotic, levofloxacin, does not have robust data showing benefit compared with placebo, but was not inferior to inhaled tobramycin [86]. It is now challenging to undertake clinical trials in this area, as the licensed treatment for tobramycin is alternate-month on/off therapy, but in clinical practice most patients are taking continuous inhaled antibiotic treatment [87, 88]. It will be difficult for further trials to be undertaken in this area, so we can only rely on network meta-analysis to compare treatments [86].

Inhaled tobramycin on alternate months or regular colistin are both acceptable initial therapies to prevent exacerbations in people with *P. aeruginosa* infection. If using the alternate-month tobramycin regime, any further exacerbations should result in consideration of colistin, aztreonam or levofloxacin on the alternate months so that inhaled antibiotic therapy is continuous. Other combinations should be considered individually based on microbiology, disease severity, frequency of exacerbation and tolerance of inhaled therapies. This aspect of care needs to be carefully individualised.

Azithromycin is usually reserved until chronic *P. aeruginosa* infection has occurred and is recommended for all patients with chronic *P. aeruginosa* infection if they can tolerate it [89]. There is some evidence that azithromycin reduces exacerbations in people who do not have chronic *P. aeruginosa* infection, and it should be considered for frequent exacerbators, regardless of infection type [89]. Azithromycin is an effective therapy, but it is unclear whether its effect is maintained with long-term treatment, and there have been recent concerns about an interaction with tobramycin [90, 91].

What are the exacerbation reductions with new modulator therapies?

CFTR modulator therapies (ivacaftor in patients with a G551D mutation and ivacaftor/lumacaftor in homozygous F508del patients) improve lung function and QoL and reduce pulmonary exacerbations (table 3) [68, 92]. The effect on exacerbations in both groups is

Table 2. Effects of antibiotic therapies that reduce pulmonary exacerbations

Treatment	Exacerbations	QoL	FEV_1	Other effects
Tobramycin	Decreased	Increased	Increased	
Aztreonam	Decreased	Increased	Increased	
Levofloxacin	Decreased	Increased	Increased	Dysgeusia
Azithromycin	Decreased	Increased	Increased	Hearing problems
Flucloxacillin	ND	ND	ND	Nausea

No placebo-controlled trial data are available for colistin. Note that it is difficult to determine the effect sizes. Tobramycin, aztreonam and levofloxacin have the most evidence of a reduction in exacerbations and ~5% improvement in FEV_1. ND: no data available. Information from [35, 82–91].

Table 3. CF transmembrane conductance regulator modulator therapies that reduce pulmonary exacerbations

Treatment	Exacerbations	QoL	FEV_1	Other effects
Ivacaftor	Decreased 40%	Increased	Increased 10%	Weight gain
Ivacaftor/lumacaftor	Decreased 30%	Increased	Increased 3%	Weight gain, respiratory AEs

Information from [68, 92–95].

similar, although there was a smaller improvement in FEV_1 in the ivacaftor/lumacaftor trials in homozygous F508del patients [93, 94]. A recent analysis indicated that an improvement in FEV_1 and reduction in exacerbations in response to the drugs in this group are not strongly coupled with patients demonstrating improvements in exacerbations independent of FEV_1 response [95]. This effect on exacerbation has recently been confirmed in a clinical trial of tezacaftor/ivacaftor in homozygous F508del patients.

Modulator therapies are clearly indicated to reduce future exacerbations in indicated mutations, and this is a primary reason for their prescription. It is hoped that further combinations of drugs that modulate CFTR function will further reduce exacerbation frequency, attenuate FEV_1 decline and improve QoL. This is likely to deliver additional survival advantages [96].

Are there strategies for stopping or substituting therapies that prevent exacerbations?

People with CF are faced with almost overwhelming polypharmacy, particularly as the disease progresses. Many of these therapies as outlined above are to prevent exacerbations. Adherence in this field is very challenging, and careful thought in individual patients is required to optimise preventative therapy [97]. The development of these therapies in clinical trials has been to add them on to current treatment. This has been translated into clinical practice, and many individuals are asked to take multiple inhaled and oral drugs. There is an urgent need to reconsider how these drugs are used in combination, particularly with the advent of CFTR modulator therapies. Opportunities to prioritise, stop or substitute therapies for individual patients should be considered. Comparative effectiveness trials and registry-based studies are required to help with this decision making.

Summary and conclusions

Pulmonary exacerbations have a negative impact on important patient outcomes in people with CF. Prevention of these exacerbations should be the top priority for people with CF with the support of their multidisciplinary teams. Preventative treatment should be personalised to maximise efficacy and optimise adherence. When exacerbations occur, they should be treated promptly with antibiotics and optimisation of other therapies. The choice of antibiotics should usually include two drugs in different classes for treatment of *P. aeruginosa* and other Gram-negative nonfermenters. In all cases, antibiotic therapy should be chosen according to physician and patient experience, tolerance of specific antibiotics and an overall understanding of the probable susceptibility of the particular

 https://doi.org/10.1183/2312508X.10016616

bacterium to a particular class of antibiotics. *In vitro* sensitivity testing does not appear to add benefit to antibiotic choice, but further research is needed to determine whether there are more informative methodologies to improve this.

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Disclosures: J.S. Elborn has received consultancy payments from Vertex, Horizon, Galapagos/Abbvie, Celtaxsys and Corbus. He holds grant funding in collaboration with Novartis, Gilead and Ployfor.

 https://doi.org/10.1183/2312508X.10016616

Chapter 13

Non-cystic fibrosis bronchiectasis: treatment and prevention of pulmonary exacerbations

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Prevention and treatment of exacerbations are vital for the effective management of bronchiectasis. There is a lack of clinical trials to help guide clinicians with regard to evidence-based interventions for patients with bronchiectasis. Recent clinical trial evidence supports the use of long-term oral macrolide therapy to prevent exacerbations in patients with and without chronic *Pseudomonas* infection. There is less robust evidence for therapies used to treat exacerbations in bronchiectasis, and for other therapies that aim to prevent exacerbations, including inhaled antibiotics. As a result, clinical practice varies significantly among clinicians. The development of large international databases should increase the evidence base for interventions. International guidelines are due to be published in 2017 that will update best-practice management of patients with bronchiectasis.

Cite as: Harrison MJ, Haworth CS. Non-cystic fibrosis bronchiectasis: treatment and prevention of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 181–198 [https://doi.org/10.1183/2312508X.10016716].

Exacerbations of bronchiectasis are associated with reduced QoL [1, 2] and increased mortality [2], and place a significant burden on global healthcare systems [3, 4]. Historically, research in bronchiectasis has been relatively sparse compared with other commonly encountered lung diseases, resulting in a lack of evidence-based treatments for preventing and treating exacerbations in people with bronchiectasis. This chapter outlines broad principles that underpin the treatment and prevention of exacerbations of bronchiectasis and reviews the currently available evidence.

Treatment

Identifying the exacerbation

Current guidelines advocate starting treatment if there is an acute deterioration (usually over several days) with worsening local symptoms (cough, increased sputum volume or

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change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset [5]. It is important to encourage individual patients to identify which symptoms are typical of exacerbation for themselves to allow prompt identification and initiation of treatment.

Identifying the organism/trigger

A sputum sample should be obtained for microbiological culture and antibiotic susceptibility testing prior to commencing antibiotics for all exacerbations. Identification of a "target" organism using previous microbiological culture results should inform initial antibiotic choices, which can subsequently be tailored according to the results of contemporaneous sputum culture and clinical response. Empirical first-line therapy in the absence of previous microbiological culture results will vary depending on local microbiological advice according to local patterns of infection.

The most common bacterial species identified in sputum are *Haemophilus influenzae* and *Pseudomonas aeruginosa*, with *Staphylococcus aureus*, *Streptococcus* spp., NTM, *Moraxella* spp., *Prevotella* spp. and *Veillonella* spp. less commonly seen [6–10]. While *H. influenzae* is often more frequently identified, chronic infection with *P. aeruginosa* is associated with increased symptom scores, increased frequency of exacerbations, a sharper decline in lung function and increased mortality risk [2, 11–18].

While viruses are implicated in exacerbations of COPD and asthma, there is limited evidence examining the role of viruses in exacerbations of bronchiectasis. Gao *et al.* [19] demonstrated the presence of viruses by PCR in 49 out of 100 patients during an exacerbation compared with 11 out of 58 patients in the steady state. Kapur *et al.* [20] detected viruses in 37 out of 77 nasopharyngeal aspirates in children with an exacerbation of bronchiectasis. Both studies suggested that virus-positive exacerbations are more likely to cause a more severe clinical deterioration compared with virus-negative exacerbations. There are no studies of the use of antiviral drugs for the prevention or treatment of exacerbations of bronchiectasis, and available antiviral drugs should be used according to local guidelines.

Antibiotics

Antibiotics are the mainstay of treatment of exacerbations in bronchiectasis. While there has been a lack of RCTs evaluating the efficacy of antibiotics, the optimal number and dosing regimens of antibiotics to use, and the length of treatment during exacerbations of bronchiectasis, there are several studies that demonstrate a benefit in terms of reduced inflammatory markers, reduced sputum viscosity, reduced sputum bacterial load and improved symptoms scores [11, 21]. Clinical experience suggests that longer courses of antibiotics at higher doses provide better outcomes than shorter courses, particularly for the treatment of *P. aeruginosa* and resistant organisms. This may reflect the difficulty in attaining high concentrations of antibiotics in the bronchiectatic airway in the context of resistant organisms that may be protected by biofilm. While a shorter duration of treatment may be appropriate for patients who display a rapid response to treatment with evidence of a susceptible organism on culture, we advocate a treatment duration of 14 days, in line with current guidelines [5]. In the only trial of inhaled antibiotics for the treatment of exacerbations, Bilton *et al.* [22] showed no clinical benefit of addition of inhaled

 https://doi.org/10.1183/2312508X.10016716

tobramycin to oral ciprofloxacin compared with placebo and oral ciprofloxacin, with a significant increase in wheeze in the tobramycin cohort.

Oral antibiotics

Oral antibiotic treatment is the first-line treatment for exacerbations of bronchiectasis unless the patient is very unwell or is known to harbour resistant organisms that are unlikely to respond to oral treatments. Table 1 lists suggested oral antibiotic choices for treatment of exacerbations based on microbiological culture testing.

Susceptibility testing

Current guidelines recommend the use of contemporaneous antibiotic susceptibility testing, where available, to guide the physician's antibiotic choices [5]. With regard to *Pseudomonas*

Table 1. Oral antibiotics for treatment of exacerbations of bronchiectasis based on microbiological culture results

Organism	First-line antibiotics	Second-line antibiotics
Haemophilus influenzae	Amoxicillin 500 mg–1 g three times daily Doxycycline 100 mg twice daily Trimethoprim 200 mg twice daily	Co-amoxiclav 625 mg three times daily Moxifloxacin 400 mg once daily
Streptococcus pneumoniae	Amoxicillin 500 mg–1 g three times daily Doxycycline 100 mg twice daily Trimethoprim 200 mg twice daily	Clarithromycin 500 mg twice daily Moxifloxacin 400 mg once daily
Moraxella catarrhalis	Amoxicillin 500 mg–1 g three times daily Doxycycline 100 mg twice daily Trimethoprim 200 mg twice daily Clarithromycin 500 mg twice daily	Ciprofloxacin 750 mg twice daily Co-amoxiclav 625 mg three times daily
Pseudomonas aeruginosa	Ciprofloxacin 750 mg twice daily[#]	No effective oral second-line agent Intravenous therapy
Coliforms	Co-amoxiclav 625 mg three times daily	Ciprofloxacin 750 mg twice daily
Staphylococcus aureus	Flucloxacillin 500–1000 mg four times daily	Doxycycline 100 mg twice daily Trimethoprim 200 mg twice daily Clarithromycin 500 mg twice daily Co-amoxiclav 625 mg three times daily
MRSA	Rifampicin 400–600 mg once daily and fusidic acid 500 mg three times daily[#]	Doxycycline 100 mg twice daily Trimethoprim 200 mg twice daily
Stenotrophomonas maltophilia	Cotrimoxazole 960 mg twice daily	Minocycline 100 mg twice daily
Achromobacter xylosoxidans	Cotrimoxazole 960 mg twice daily[#]	Minocycline 100 mg twice daily

[#]: consider eradication therapy if first growth of organism (see table 2 for suggested intravenous treatment options).

spp., the role of antibiotic susceptibility testing is controversial. Studies have shown significant variability in the results of antibiotic susceptibility testing in bronchiectasis [23], with poor correlation between *in vitro* susceptibility testing of sputum at the onset of exacerbation and clinical outcomes [24, 25]. GILLHAM *et al.* [23] found phenotypic variation in antibiotic susceptibility patterns among multiple *Pseudomonas* colony morphotypes identified in sputum samples from 31 patients with bronchiectasis. An RCT comparing multiple combination bactericidal testing *versus* clinician preference to guide antibiotic choices to manage CF pulmonary exacerbations demonstrated no differences in outcome [26]. An alternative strategy for choosing antibiotics is to use antibiotics that have produced a clinical response in that patient in the past.

i.v. *antibiotics*

There are no RCTs evaluating *i.v.* antibiotic treatment in bronchiectasis. *i.v.* antibiotics are recommended for patients with severe exacerbation or in patients who have failed to respond to oral treatments. Table 2 lists suggested *i.v.* antibiotic choices for patients according to sputum microbiology.

Treatment with a single *i.v.* antibiotic may be sufficient for patients without *P. aeruginosa* and for those with fully sensitive *P. aeruginosa* on culture. If there is evidence of resistance on antibiotic susceptibility testing, or if the patient is likely to require recurrent courses of *i.v.* antibiotics over time that might facilitate the development of resistance, dual therapy is recommended [5]. The combination of a β-lactam and an aminoglycoside may provide additional benefit due to the reported synergy between these antibiotic classes [27]. Our practice is to use two *i.v.* antibiotics, ideally with differing mechanisms of action, such as a β-lactam in combination with an aminoglycoside. Table 3 shows a suggested approach to treatment of exacerbations associated with *P. aeruginosa*.

Eradication therapy for a first isolate of P. aeruginosa

There is limited clinical trial evidence to support eradication therapy in patients with bronchiectasis and a first isolate of *P. aeruginosa*. In the only prospective study of eradication in bronchiectasis, ORRIOLS *et al.* [28] recently performed a 15-month, single-masked RCT in 35 patients with a first isolate of *P. aeruginosa* infection. The study compared an eradication regimen of 2 weeks of *i.v.* ceftazidime and tobramycin, followed by either 3 months of 300 mg of nebulised tobramycin twice daily or placebo. After 12 months of follow-up, 54% of patients were free of *P. aeruginosa* in the tobramycin group compared with 29% in the placebo group, with a significant reduction in the number of exacerbations in the tobramycin-treated patients *versus* placebo (1.27±1.62 *versus* 2.5±1.63 (mean±SD); p=0.04). The median time to recurrence of *P. aeruginosa* was longer and the number of hospital admissions was lower in the tobramycin-treated patients. There were no safety concerns and no evidence of tobramycin-resistant organisms during the study follow-up. There was a higher rate of discontinuation in the tobramycin arm (five patients) *versus* the control arm (two patients). The subgroup of patients who discontinued were older and had more severe lung disease. Despite the paucity of clinical trial data, there is a strong rationale for eradication treatment in an attempt to avoid or delay the known poorer clinical outcomes associated with chronic *P. aeruginosa* infection [2, 12–15, 17]. Current guidelines recommend attempted eradication at the time of identification of the first isolate of *P. aeruginosa*, as shown in figure 1. Recent evidence suggesting that sputum becomes spontaneously clear of *P. aeruginosa* in ∼20% of patients without any intervention [18] emphasises the importance of regular sputum sampling in patients with bronchiectasis both to promptly identify *P. aeruginosa* in the first instance and to identify whether it has

 https://doi.org/10.1183/2312508X.10016716

Table 2. Intravenous antibiotics for the treatment of exacerbations of bronchiectasis according to sputum microbiology

Organism	First-line antibiotics	Second-line antibiotics
Haemophilus influenza*, *Streptococcus pneumoniae*, *Moraxella catarrhalis	Cefuroxime 1.5 g three times daily	Piperacillin with tazobactam 4.5 g three times daily
Pseudomonas aeruginosa	One of the following: Ceftazidime 2 g three times daily Aztreonam 1 g three times daily Piperacillin with tazobactam 4.5 g three times daily Meropenem 1 g three times daily Plus tobramycin[#] or colistimethate sodium 1 MIU three times daily	See table 3 for further recommendations regarding *i.v.* treatment for *P. aeruginosa*
Coliforms	Cefuroxime 1.5 g three times daily	Piperacillin with tazobactam 4.5 g three times daily Aztreonam 2 g three times daily Meropenem 1 g three times daily
Staphylococcus aureus	Flucloxacillin 1–2 g four times daily	Piperacillin with tazobactam 4.5 g three times daily
MRSA	Vancomycin[#]	Teicoplanin[#] Linezolid 600 mg twice daily Tigecycline 50 mg twice daily Fosfomycin 4 g three times daily
Stenotrophomonas maltophilia	Co-trimoxazole 1.44 g twice daily	Tigecycline 50 mg twice daily Colistimethate sodium 1 MIU three times daily
Achromobacter xylosoxidans	Piperacillin with tazobactam 4.5 g three times daily[¶]	Meropenem 1 g three times daily Tigecycline 50 mg twice daily Ceftazidime 2 g three times daily

MIU: million international units. [#]: variable dose according to body weight, renal function and drug levels. [¶]: typically multiresistant organisms; dual therapy may be required.

cleared in subsequent samples. While there is recent evidence supporting the use of nebulised tobramycin [28], there is no evidence to suggest that any particular eradication regimen is superior to the others.

Antibiotic infusions

Given the time-dependent antibacterial action of β-lactam antibiotics [29, 30], it seems logical to use continuous infusions to maximise the time above minimum inhibitory concentration during treatment with *i.v.* β-lactam antibiotics. Hubert *et al.* [31] compared continuous infusion with infusion three times daily of ceftazidime in patients with CF and a resistant organism on sputum culture. While there was no difference in tolerability between the two modes of antibiotic administration, there were greater improvements in lung function and a longer duration to next exacerbation following treatment with continuous infusions. However, delivering antibiotics *via* continuous infusion can be

Table 3. Intravenous antibiotics for treatment of exacerbations of bronchiectasis associated with *Pseudomonas aeruginosa*

First-line combination		Second-line agents[¶]	Third-line agents	Add-on options
Antibiotic 1[#]	Antibiotic 2			
Ceftazidime 2 g three times daily Piperacillin/tazobactam 4.5 g three times daily Meropenem 1 g three times daily Aztreonam 1 g three times daily	Tobramycin: as per local dosing guidelines Colistimethate sodium 1 MIU three times daily Another agent from antibiotic 1	Fosfomycin 4 g three times daily (or four times daily) Imipenem and cilastatin 500 mg–1 g from twice daily to four times daily	Ciprofloxacin 400 mg twice daily[+]	Continuous infusions of antibiotic 1 Nebulised antibiotics[§]

MIU: million international units. [#]: can be given as a bolus, infusion or continuous infusion; [¶]: can replace either antibiotic 1 or 2, or be used in addition in the case of fosfomycin; [+]: ciprofloxacin should be reserved for oral use where possible and used in conjunction with two other agents, if possible; [§]: use of nebulised aminoglycoside may be helpful where renal toxicity or ototoxicity is an issue.

time-consuming for healthcare providers and burdensome for the patient. We recommend a continuous infusion of *i.v.* β-lactam antibiotics if there is a suboptimal clinical response to *i.v.* bolus dosing or in the context of resistant organisms.

Corticosteroids

There are no studies of inhaled corticosteroids (ICSs) or systemic corticosteroids in the treatment of exacerbations of bronchiectasis. Current guidelines recommend their use only when treating coexistent asthma or COPD.

Airway clearance techniques

There are no studies examining the role of airway clearance techniques (ACTs) in the treatment of exacerbations of bronchiectasis. Current guidelines recommend that ACTs should continue during an exacerbation and that the addition of manual techniques should be considered [5]. ACTs may need to be temporarily suspended or modified in the presence of haemoptysis. Conversely, many patients will derive a benefit from increased frequency and intensity of ACTs during an exacerbation to aid with clearance of increased volumes of more viscous sputum.

Mucoactive drugs

There are no studies examining the role of mucoactive drugs (carbocysteine, *N*-acetylcysteine, β-agonists, aminophylline, nebulised isotonic or hypertonic saline, inhaled mannitol) in the treatment of exacerbations of bronchiectasis. Oral and inhaled mucoactive therapies are used as maintenance treatments to aid with sputum expectoration in clinically stable patients with bronchiectasis. Patients undergoing an exacerbation may derive a benefit from increasing the dose or frequency of administration of these drugs to maximise

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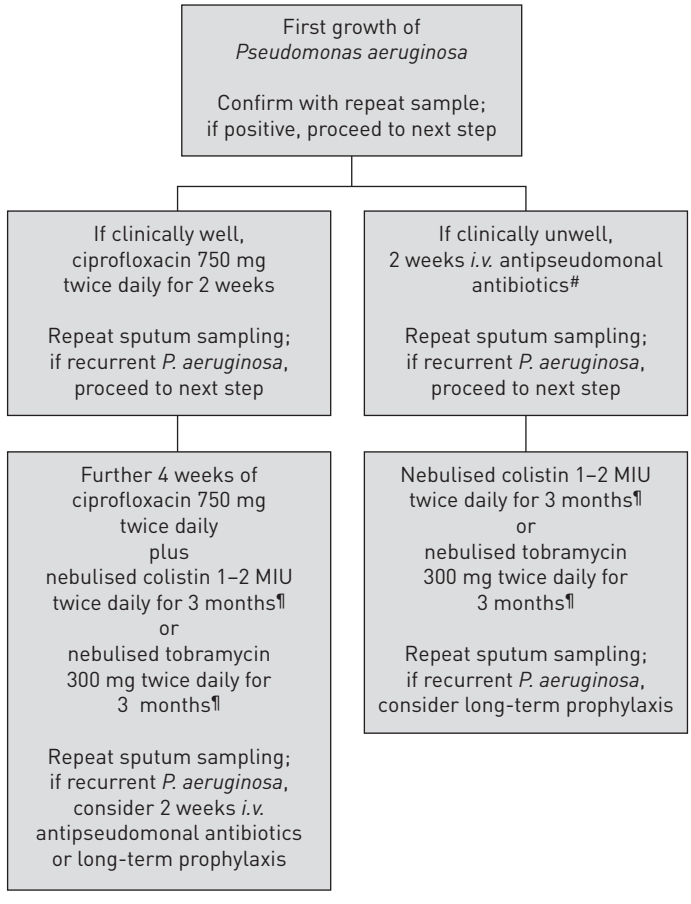

Figure 1. Suggested eradication algorithm for treatment of the first isolate of *Pseudomonas aeruginosa*. *i.v.*: intravenous; MIU: million international units. #: see table 3; ¶: requires supervised challenge test, given the risk of bronchoconstriction.

their impact during an exacerbation. Optimising hydration status using oral or *i.v.* fluids may also improve sputum expectoration in these patients.

Prevention

Until recently, there was a paucity of data surrounding interventions to prevent exacerbations in bronchiectasis. While recent trials have provided a stronger evidence base for oral macrolide therapy and inhaled antibiotic therapy, there are still no licensed products available for the prevention of exacerbations.

Cole's model of the vicious cycle of inflammation and lung damage (figure 2) provides a useful framework for understanding the target of the treatments used to prevent exacerbations [32].

Current strategies to prevent exacerbations include reducing the bacterial burden within the airways, reducing airways inflammation, optimising clearance of secretions and treating any identifiable underlying disorder, as described recently by Chalmers *et al.* [33] (figure 3). It

is important to ensure that appropriate investigation of the underlying cause of the bronchiectasis has taken place, as specific therapies can alter the clinical course significantly. For example, patients with hypogammaglobulinaemia and frequent exacerbations should be reviewed by an immunologist and considered for a trial of immunoglobulin therapy. At each consultation, a review of adherence to prescribed therapies, including ACTs, should also be performed.

Antibiotics

Daily oral or inhaled antibiotics are commonly used in an attempt to reduce bacterial abundance and airway inflammation, and to prevent exacerbations. The earliest studies from the 1950s and 1960s examining the use of long-term antibiotics were poorly designed, but suggested clinical benefits in patients with bronchiectasis treated with long-term penicillins and tetracyclines [34–36]. Further studies from the 1990s failed to show a reduction in exacerbations with high-dose amoxicillin [37], and the use of long-term ciprofloxacin was associated with the development of drug-resistant strains of *P. aeruginosa* [38]. Current guidelines, written in 2010, recommend the use of long-term antibiotics, with the antibiotic selected based on sputum microbiology, in patients having three or more exacerbations per year that require antibiotic treatment and in patients with fewer exacerbations that cause significant morbidity [5]. The guidelines noted preliminary data suggesting that macrolides have disease-modifying activity and recommended clinical trials to evaluate this further. Three subsequent clinical trials have now demonstrated a clear benefit for the use of long-term oral macrolide therapy in preventing exacerbations in adults with bronchiectasis [39–41].

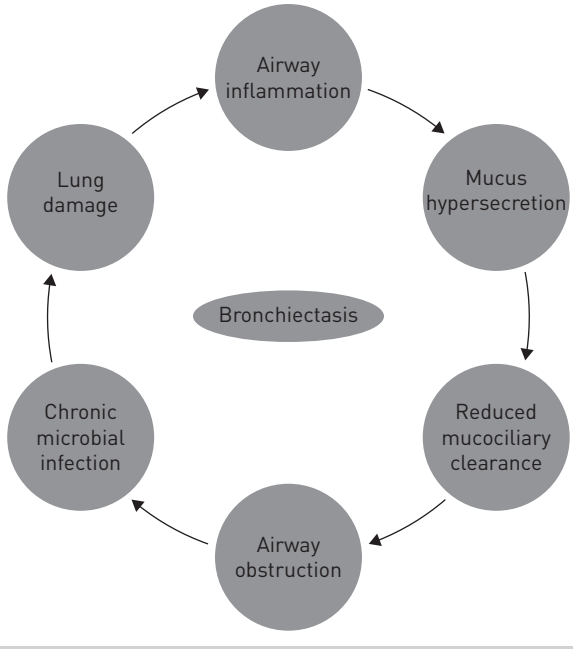

Figure 2. The vicious cycle of inflammation in bronchiectasis.

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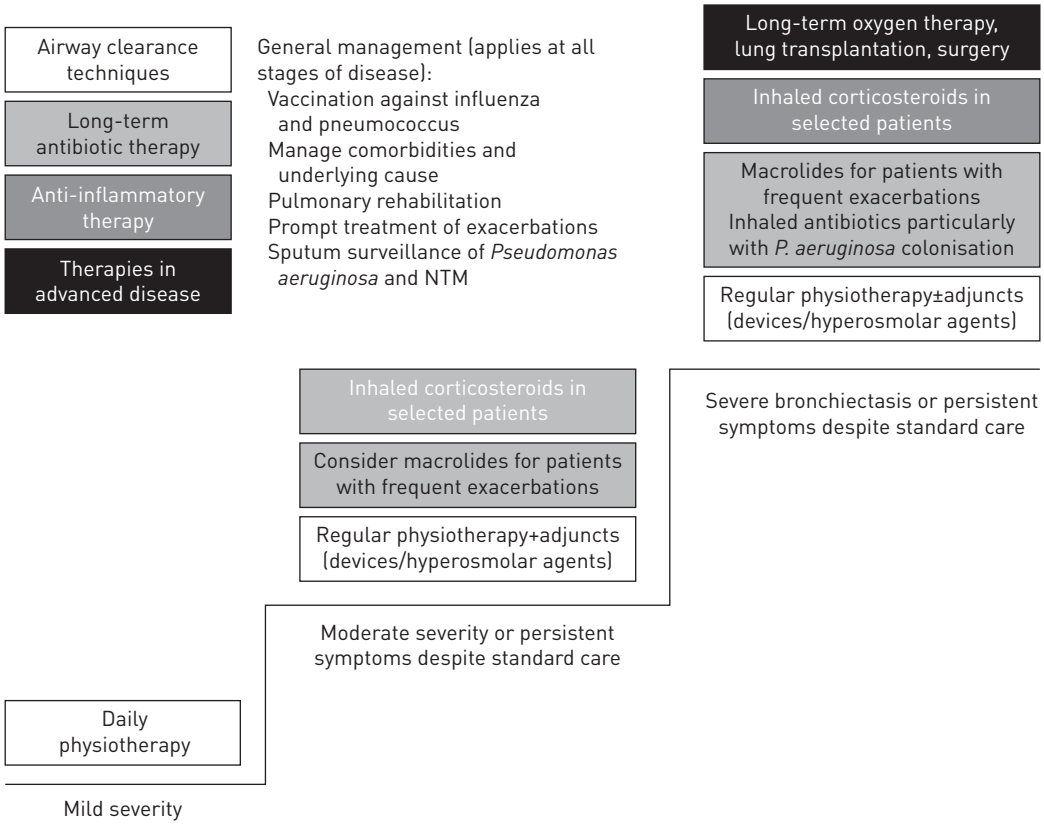
Airway clearance techniques
Long-term antibiotic therapy
Anti-inflammatory therapy
Therapies in advanced disease
General management (applies at all stages of disease):
Vaccination against influenza and pneumococcus
Manage comorbidities and underlying cause
Pulmonary rehabilitation
Prompt treatment of exacerbations
Sputum surveillance of Pseudomonas aeruginosa and NTM
Long-term oxygen therapy, lung transplantation, surgery
Inhaled corticosteroids in selected patients
Macrolides for patients with frequent exacerbations
Inhaled antibiotics particularly with P. aeruginosa colonisation
Regular physiotherapy±adjuncts (devices/hyperosmolar agents)
Severe bronchiectasis or persistent symptoms despite standard care
Inhaled corticosteroids in selected patients
Consider macrolides for patients with frequent exacerbations
Regular physiotherapy+adjuncts (devices/hyperosmolar agents)
Moderate severity or persistent symptoms despite standard care
Daily physiotherapy
Mild severity

Figure 3. The stepwise management of non-CF bronchiectasis. Alternative oral antibiotics such as β-lactams or tetracyclines may be appropriate for patients intolerant of or not suitable for macrolides. Reproduced and modified from [33] with permission.

Oral antibiotics

The EMBRACE (Effectiveness of macrolides in patients with bronchiectasis using azithromycin to control exacerbations) trial was the first RCT of macrolides in bronchiectasis [39]. The study comprised a randomised, double-blinded, placebo-controlled 6-month comparison of azithromycin 500 mg three times weekly with placebo in 141 patients with bronchiectasis and at least one exacerbation in the previous 12 months. The study authors reported a significant reduction in the number of exacerbations in the azithromycin arm compared with placebo (0.59 *versus* 1.57, incidence rate ratio 0.38, 95% CI 0.26–0.54; p<0.0001).

The BAT (Bronchiectasis and long-term azithromycin treatment) trial was a double-blinded 12-month RCT comparing azithromycin 250 mg once daily with placebo in 83 patients with bronchiectasis and three or more exacerbations in the previous 12 months [40]. This study showed a decrease in exacerbation rates in the azithromycin group, with 46% having at least one exacerbation compared with 80% in the placebo group (hazard ratio 0.29, 95% CI 0.16–0.51). There was a significant increase in gastrointestinal side-effects noted in the treatment arm compared with placebo (40% *versus* 5%, relative risk 7.44 for abdominal pain and 8.36 for diarrhoea), although the side-effects did not result in discontinuation of

treatment. The rates of macrolide resistance were 88% in the azithromycin arm compared with 26% in the placebo group.

The BLESS (Bronchiectasis and low-dose erythromycin study) trial was a double-blinded RCT examining the use of twice-daily erythromycin compared with placebo over a 12-month period in 107 patients with bronchiectasis with two or more exacerbations in the previous year [41]. The study authors reported a modest decrease in the mean rate of pulmonary exacerbations overall (1.29, 95% CI 0.93–1.65, *versus* 1.97, 95% CI 1.45–2.48, exacerbations per patient per year; incidence rate ratio 0.57, 95% CI 0.42–0.77; p=0.003), and in a subgroup with *P. aeruginosa* (mean difference 1.32, 95% CI 0.19–2.46; p=0.02). There was also a modest decrease in the rate of lung function decline (mean decrease 2.2% of FEV_1 % predicted) compared with placebo. There was a significant increase in the rate of macrolide resistance in oropharyngeal streptococci in the treatment arm *versus* the placebo arm (median difference 25.5%; p<0.001).

Taken together, these trials showed that long-term oral macrolide therapy is effective in preventing exacerbations in bronchiectasis. While there was a high rate of gastrointestinal side-effects, these appeared to be tolerable, and there was no evidence of cardiac arrhythmia or ototoxicity reported in any of the trials. The increased rate of macrolide resistance is a concern, and it remains to be seen what impact this will have in patients receiving long-term macrolide therapy. Despite this concern, we recommend the use of oral azithromycin 250 mg three times weekly (titrating according to tolerability and clinical response) as a first-line treatment in patients with three or more exacerbations per year without evidence of chronic *P. aeruginosa* infection. If a macrolide is contraindicated or is not tolerated, a trial of an alternative oral antibiotic selected based on sputum microbiology culture is reasonable, as recommended in the current guidelines [5]. We recommend adding long-term oral macrolide therapy in patients with chronic *P. aeruginosa* infection whose exacerbation frequency is not sufficiently reduced on inhaled antibiotics (see section on Inhaled antibiotics). Of note, there was a relatively low incidence of chronic infection with *P. aeruginosa* across the trials; further studies examining macrolide use in larger populations of patients with chronic infection with *P. aeruginosa* would help to clarify the benefit of macrolides in this group.

Patients should be monitored closely for the development of tinnitus and evidence of hepatotoxicity, and should have a baseline ECG and follow-up ECG monitoring to screen for evidence of QT interval prolongation, particularly if there is a history of cardiovascular disease. Serial sputum sampling to screen for evidence of mycobacterial infection is recommended prior to the commencement of macrolides. Close monitoring of sputum microbiology and infection frequency may allow identification of clinically significant resistance.

Inhaled antibiotics

The inhaled route results in high concentrations of antibiotic within the airway and reduces the risk of side-effects due to significantly reduced absorption and systemic exposure. Inhaled antibiotics targeting *P. aeruginosa* have proven efficacy in improving clinical outcomes in people with CF [42, 43]. Given the similar poor outcomes associated with chronic *P. aeruginosa* infection in bronchiectasis, is not surprising that, to date, the inhaled antibiotics that have been trialled in patients with bronchiectasis have predominantly targeted *P. aeruginosa*. Unfortunately, currently none of the trials of inhaled antibiotics has resulted in the approval for licensing of any inhaled antibiotics for the treatment

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of bronchiectasis. HAWORTH *et al.* [44] reported a randomised, placebo-controlled study assessing the efficacy and safety of inhaled colistin in 144 patients with bronchiectasis and *P. aeruginosa* infection over a maximum of 6 months or until first exacerbation. While the primary end-point (time to first exacerbation) did not achieve statistical significance, there were significant improvements in *P. aeruginosa* density and St George's Respiratory Questionnaire scores over the study period. Moreover, there was a statistically significant improvement in time to exacerbation (168 days in the colistin-treated patients compared with 103 days in those receiving placebo; p=0.028) in a subgroup who demonstrated >80% adherence (recorded electronically *via* specially adapted nebuliser devices). Inhaled colistin was well tolerated and there were no safety concerns. While this study did not meet its primary end-point, it does provide evidence for improvements in clinically important outcomes, including a reduction in exacerbations in patients who are adherent to inhaled colistin treatment.

MURRAY *et al.* [45] reported a 12-month RCT comparing gentamicin 80 mg nebulised twice daily with 0.9% normal saline placebo in 57 patients with bronchiectasis and predominantly *H. influenzae* and *P. aeruginosa*. The study found significant improvements in time to first exacerbation (median 120 days, range 87–161.5 days, *versus* median 61.5 days, range 20.7–122.7 days; p=0.02) and exacerbation frequency (0, range 0–1, *versus* 1.5, range 1–2; p<0.0001) in patients treated with gentamicin *versus* placebo. There were no reported safety concerns or observed development of gentamicin resistance. Nebulised gentamicin was also associated with significant reductions in bacterial density of non-*P. aeruginosa* organisms, with a 93% eradication rate in patients infected with other pathogens (compared with a 31% eradication rate in patients infected with *P. aeruginosa*). This study provided evidence for the use of nebulised gentamicin in preventing exacerbations in patients with bronchiectasis, and suggests that it may be particularly effective in those from whom organisms other than *P. aeruginosa* are cultured.

A number of studies have demonstrated the safety, efficacy and tolerability of inhaled tobramycin in patients with CF and chronic infection with *P. aeruginosa* [43, 46, 47]. Trials of various doses of inhaled tobramycin in patients with bronchiectasis have been less successful. While the studies have shown improvement in clinical outcomes [48–50] without a reduction in exacerbations [50], there were high rates of discontinuation of the drug due to problems with tolerability [49, 50] and concerns regarding the development of tobramycin resistance [48, 49]. This may reflect difficulties in study design for these trials, the lack of dose-finding studies prior to phase III trials and a more elderly study population compared with CF studies, resulting in decreased tolerability of the study drug [51]. A study examining the addition of inhaled tobramycin to oral ciprofloxacin for treatment of AEs of bronchiectasis failed to show an additional clinical benefit, which may have been due to a marked increase in wheeze in the treatment arm [22].

Two large, double-blinded RCTs AIR-BX1 and AIR-BX2 (Safety and effectiveness of AZLI (an inhaled antibiotic) in adults with non-cystic fibrosis bronchiectasis) examined the safety and efficacy of inhaled aztreonam 75 mg three times daily (1 month on, 1 month off, with a 1-month washout period) *versus* placebo in 540 patients with bronchiectasis and Gram-negative organisms on culture (~80% *P. aeruginosa*) [52]. The primary end-point of change in QoL Bronchiectasis score at 4 weeks achieved statistical significance in one of the trials (AIR-BX2), but was not deemed to be a clinically significant change. Adverse events and discontinuation due to adverse events were more common in the treatment arm of both trials. There are some concerns regarding the study design for these trials; further

trials of a longer duration with improved microbiological enrolment criteria and using an exacerbation-defined primary end-point may be useful.

Two phase II studies of different formulations of inhaled ciprofloxacin demonstrated safety and tolerability in patients with bronchiectasis and chronic *P. aeruginosa* infection [53, 54]. The trials reported statistically significant improvements in microbiological [53, 54] and clinically important [53] outcomes with inhaled ciprofloxacin *versus* placebo. Phase III studies are due to be reported in the near future.

The current evidence from trials of inhaled antibiotics supports the use of inhaled colistin as a first-line agent and inhaled gentamicin as a second-line agent in patients with bronchiectasis and chronic infection with *P. aeruginosa*. Monitoring for evidence of drug toxicity is important with inhaled aminoglycosides, particularly where azithromycin and aminoglycosides are co-prescribed (increased risk of ototoxicity). It is hoped that the phase III trials of inhaled ciprofloxacin will result in a licensed therapy for patients with bronchiectasis and chronic *P. aeruginosa* infection. For patients with chronic infection with organisms other than *P. aeruginosa*, we recommend a trial of inhaled gentamicin if a trial of long-term oral macrolide therapy does not sufficiently reduce exacerbation frequency.

Airway clearance techniques

Current guidelines recommend that all patients with bronchiectasis should be trained in the performance of ACTs [5]. There is no evidence that any particular technique is better than another, and the regimen should be tailored to the individual patient's abilities and preferences, and guided by the location and extent of bronchiectasis on CT scanning. The only RCT of ACT in bronchiectasis compared twice-daily chest physiotherapy using an oscillatory positive expiratory pressure device with no chest physiotherapy in a 3-month crossover study design [55]. This study showed significantly improved sputum volume, symptoms scores and exercise capacity, but no impact on microbiology, lung function or exacerbation frequency (noting that exacerbation rate was not a predefined study end-point).

Pulmonary rehabilitation/exercise training

Current guidelines recommend that pulmonary rehabilitation be offered to individuals who have breathlessness affecting their activities of daily living and that inspiratory muscle training can be used in conjunction with conventional pulmonary rehabilitation to enhance the maintenance of the training effect. Lee *et al.* [56] performed the only study examining the effect of exercise training on exacerbations in bronchiectasis. Patients were randomised to participate in an individualised, twice-weekly exercise programme for 8 weeks or to receive information regarding the benefits of exercise in bronchiectasis with twice-weekly telephone support and were followed over a 12-month period. Patients receiving exercise training had a reduced exacerbation rate compared with the control group (median 1, interquartile range 1–3, *versus* median 2, interquartile range 1–3; p=0.012) and an increased time to first exacerbation compared with controls (8 months, 95% CI 7–9 months, *versus* 6 months, 95% CI 5–7 months; p=0.047).

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Influenza/pneumococcal vaccine

Patients with bronchiectasis are at increased risk of influenza-triggered exacerbations, which have been shown to be more severe than nonvirus-triggered exacerbations [19]. Seasonal vaccination against influenza is recommended for all patients with bronchiectasis [5]. An open-label RCT in 167 adults with chronic lung disease (bronchiectasis and other diseases associated with bronchiectasis) compared the 23-valent pneumococcal vaccine plus influenza vaccine with influenza vaccine alone (control group) and reported a significant reduction in acute infective respiratory exacerbations in the pneumococcal vaccine group compared with the control group (OR 0.48, 95% CI 0.26–0.88; number needed to treat to benefit 6, 95% CI 4–32) over 2 years [57]. Exacerbations associated with *Streptococcus pneumoniae* are common [58], and all patients should also be offered pneumococcal vaccination following the local protocol.

Corticosteroids

There are limited trials examining the effect of ICS treatment on exacerbations in bronchiectasis. A double-blinded RCT of fluticasone 500 μg twice daily or matched placebo in 86 patients with bronchiectasis over a 52-week study period failed to show an improvement in exacerbation frequency [59]. There was a statistically significant improvement in exacerbation frequency in a subgroup of patients treated with fluticasone who were chronically infected with *P. aeruginosa* (n=12) compared with patients in the placebo arm who cultured *P. aeruginosa* (n=11) (OR 13.3, 95% CI 1.8–100.2; p=0.01). A 6-month randomised trial comparing three different doses (blinded to different doses) of inhaled fluticasone propionate with no treatment in 93 patients with bronchiectasis in whom asthma had been excluded demonstrated improved QoL scores with the higher-dose treatment (500 μg twice daily), but failed to show any improvement in exacerbation rate [60].

The effect of combined ICS/long-acting β-agonist (LABA) inhalers is unclear, with a recent Cochrane review concluding that there was insufficient evidence to recommend combined ICS/LABA in people with bronchiectasis [61]. A more recent observational study reported that salmeterol/fluticasone combined inhaled therapy reduced the number of exacerbations in 120 bronchiectasis patients (patients with COPD, asthma, significant smoking history (>10 pack-years) and current smokers were excluded) compared with a control group receiving standard care over a 6-month treatment period (1, range 0–2, *versus* 2, range 1–4; p=0.017) [62]. Larger RCTs are required to fully evaluate the role of ICS and ICS/LABA in the prevention of exacerbations. Given the lack of high-quality trial evidence of the impact of ICS/LABA on exacerbations, we recommend a trial of ICS/LABA inhaler for patients with bronchiectasis and concomitant symptoms of airway hyperresponsiveness, evidence of air trapping on CT or evidence of small airways disease on pulmonary function testing.

Mucoactive therapy

Inhaled mannitol [63], nebulised dornase alfa (recombinant human DNase I) [64] and nebulised hypertonic saline [65] have been shown to reduce the frequency of exacerbations in people with CF. Similar benefits have not been demonstrated in trials in bronchiectasis.

Most recently, an RCT of mannitol 400 mg inhaled twice daily *versus* a low-dose mannitol control in 461 patients with bronchiectasis showed a small improvement in QoL scores and

a small increase in time to first exacerbation, but did not significantly reduce exacerbation rates over 12 months [66]. A double-blinded, randomised, multicentre study of nebulised dornase alfa *versus* placebo in 349 adults with bronchiectasis over 24 weeks showed that pulmonary exacerbations were more frequent and FEV_1 decline was greater in patients who received dornase alfa [67]. Given the lack of evidence, the use of mannitol or dornase alfa is not recommended outside of CF.

An RCT randomising 40 patients with bronchiectasis to 6% hypertonic saline or isotonic saline showed modest improvements in FEV_1 % pred, QoL scores and sputum colonisation rates in both groups, with no difference in the rates of exacerbation over a 12-month follow-up period [68]. Further trials with a larger study population with more severe lung disease would be useful. In our experience, nebulised hypertonic saline can be very effective in facilitating airway clearance in those patients who tolerate a test dose without a decrease in their spirometry readings.

Oral mucolytic agents such as carbocysteine are used in clinical practice, despite the lack of clinical trial evidence of their benefit [69].

Future directions

Increased research efforts

In recent years, recognition of the need for more research in the area of bronchiectasis has resulted in an increase in clinical trials of novel therapies that may improve outcomes, including treatment and prevention of exacerbations in bronchiectasis. The development of large-scale national and international registries may offer improved stratification of patients according to phenotypic characteristics and allow increased homogeneity of patients with bronchiectasis for enrolment in future clinical trials.

There is increased focus on understanding the role of genetic factors that contribute to the development of bronchiectasis. A large-scale study (The 100 000 Genomes Project) aiming to sequence the genomes of 100 000 patients, including those with bronchiectasis who have distinct phenotypic characteristics, may reveal a new understanding of the aetiology of bronchiectasis and the factors that influence progression.

Anti-inflammatories

Inflammation, driven primarily by neutrophilic responses to acute and chronic bacterial infection, appears to play a key role in the currently accepted model of the cycle of lung damage in bronchiectasis [11, 32, 70]. It would seem logical that anti-inflammatory therapy would be a useful therapeutic option in the treatment and prevention of exacerbations of bronchiectasis. Macrolides have an immunomodulatory effect that is dose dependent, and may act to reduce exacerbation frequency by reducing inflammation [71, 72], independent of the reduction in bacterial burden [73]. A recent double-blinded RCT of a novel oral anti-inflammatory therapy (CXCR2 antagonist) in 45 patients with bronchiectasis showed a reduction in sputum neutrophil counts with a similar number of exacerbations over a 28-day study period [74]. Longer trials with novel anti-inflammatory therapies are needed to explore their role in the treatment and prevention of exacerbations.

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The lung microbiome

The advent of culture-independent molecular sequencing technology has advanced our knowledge of the lung microbiome in clinically stable patients and in exacerbations in bronchiectasis. The largest studies to date have shown that the composition of the lung microbiome is stable over time and differs little between clinically stable and exacerbating states in individuals with bronchiectasis, despite antibiotic treatments [8, 75]. This suggests that factors other than changes in bacterial abundance that are as yet undiscovered are responsible for triggering exacerbations. A further study suggests that stratification of patients with bronchiectasis on the basis of predominant bacterial taxa is more clinically informative than either conventional culture or quantitative PCR-based analysis [76]. While culture-independent techniques are increasingly employed in the field of research, the role of these methods in clinical practice is unclear. Culture-independent techniques do not provide information regarding antibiotic susceptibility, or speciation in some instances, and may not be as sensitive as culture-dependent techniques at identifying organisms that are less abundant [77]. Further larger studies are required.

Digital platforms

Advances in communications technology have made it possible to remotely monitor patients with bronchiectasis. Remote monitoring of vital signs including oxygen saturation, temperature, heart rate, blood pressure and lung function has been assessed in RCTs in patients with COPD and is currently being assessed in a large clinical trial in the UK in patients with CF (ClinicalTrials.gov number NCT02416375). This may allow remote monitoring of patients in the community, thereby minimising the need for regular travel for face-to-face consultations in the hospital and reducing the risk of cross-infection. It may also allow earlier identification of exacerbations and more rapid institution of treatment compared with current standard care.

Conclusion

Exacerbations in patients with bronchiectasis are common and are associated with reduced QoL and progression of lung disease, and represent a significant burden on global healthcare systems. Interventions to prevent and treat exacerbations are poorly supported by clinical trial data. There is a clear need for large RCTs to assess the benefit of currently used and novel therapies. The development of large international databases heralds a new era of increased research that may provide evidence-based therapies to prevent and treat exacerbations for patients with bronchiectasis.

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Disclosures: M.J. Harrison reports receiving personal fees from Vertex Pharmaceuticals, outside the submitted work. C.S Haworth reports receiving grants and personal fees from Vertex and Insmed, outside the submitted work. C.S. Haworth also reports receiving personal fees from Aradigm, Zambon, Gilead, Chiesi and Teva, outside the submitted work, and Raptor, during the conduct of the study.

 https://doi.org/10.1183/2312508X.10016716

IPF: treatment and prevention of pulmonary exacerbations

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AE of IPF (AE-IPF) represents episodes of acute and rapid respiratory deterioration without identifiable aetiology during the clinical course of IPF, and is burdened by a high mortality rate. It represents the leading cause of hospitalisation and death among patients with IPF. Currently available therapeutic strategies are poorly effective, and guidelines recommend best supportive care in association with high-dose steroid therapy, although the strength of the latter recommendation is weak. We review the available evidence on the treatment of AE-IPF, emphasising the therapeutic options supported by the current guidelines and describing new therapeutic approaches provided by various emerging drugs. We also examine the main points related to AE-IPF supportive care. Finally, we review the current approaches to prevention of AE-IPF.

Cite as: Condoluci C, Inchingolo R, Mastrobattista A, *et al.* IPF: treatment and prevention of pulmonary exacerbations. *In:* Burgel P-R, Contoli M, López-Campos JL eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 199–223 [https://doi.org/10.1183/2312508X.10002017].

A previous chapter in this issue of the *Monograph* [1] discusses the definitions, severity and impact of an AE of IPF (AE-IPF) (figure 1). This chapter will focus on the treatment and prevention of AEs.

Treatment of AE-IPF

AE-IPF is associated with high mortality rates [3–6], as it is unresponsive to most conventional therapies and the available treatment strategies completely lack standardisation. Nevertheless, some evidence suggests that the time between hospital admission and initiation of treatment represents a strong prognostic factor, underlining the necessity of diagnosing and treating AE-IPF as early as possible [7].

The AE-IPF management strategy consists of pharmacological and nonpharmacological treatments, and often the best clinical setting for caring for these patients is the ICU or specialised multidisciplinary centres.

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Copyright ©ERS 2017. Print ISBN: 978-1-84984-089-7. Online ISBN: 978-1-84984-090-3. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

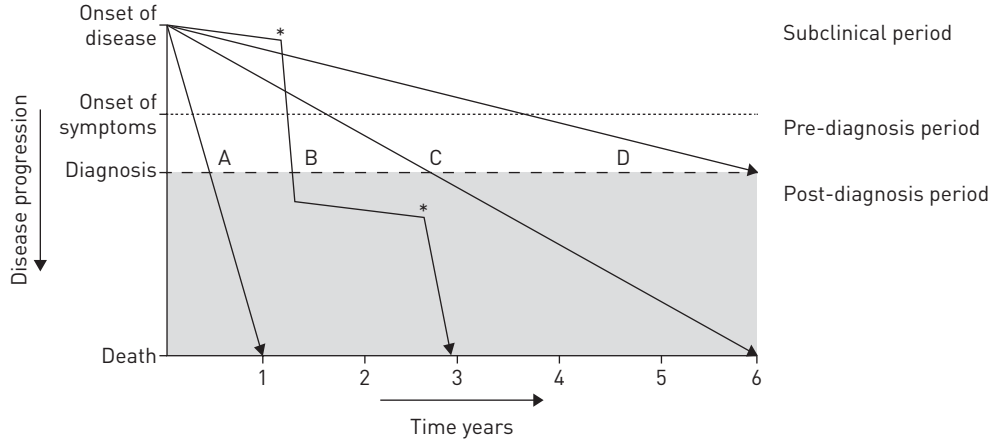

Figure 1. Potential clinical courses of IPF. The rate of decline and progression to death may be rapid (A), mixed (B) or slow (C and D), with periods of relative stability interposed with periods of acute decline (star). Reproduced and modified from [2] with permission.

Pharmacological treatment

Currently, there is no pharmacological treatment with proven and unequivocal efficacy for AE-IPF, mainly because of an imperfect understanding of the pathogenic mechanisms behind lung fibrotic processes in IPF and its rapid evolution during exacerbations. Given these limitations, current guidelines recommend best supportive care and high-dose steroids in AE-IPF treatment [8]. Nonetheless, many therapeutic approaches have been tested, and some hold promise to improve the clinical outcome in these patients (table 1).

Steroids

The mainstream pharmacological treatment of AE-IPF is the administration of high-dose corticosteroids [8]. Steroids are weakly recommended for AE-IPF by current guidelines, as the evidence supporting their use is limited, coming from observational and sometimes anecdotal studies [32].

The use of steroids is partly derived from the treatment for acute respiratory distress syndrome (ARDS), which shares with AE-IPF the same histological feature of diffuse alveolar damage, overimposed upon a usual interstitial pneumonia pattern in the case of AE-IPF [33–36]. In the guidelines, there is no mention of the dosages, route or duration of steroid administration [8, 37]. Most studies report the administration of intravenous methylprednisolone 0.5–1 g·day^{-1} for 3 consecutive days, possibly followed by oral tapering and/or administration of other immunosuppressant agents [9, 38–40].

The first report on the beneficial effects of steroid treatment in AE-IPF can be traced back to 1993, with evidence of various degrees of clinical improvement in three AE-IPF patients after *i.v.* administration of methylprednisolone 1 g·day^{-1} for 3 days, followed by a tapered dosage [9].

The IPF international working group recently reported on 75 cases published by various authors between 1997 and 2012 that support the use of steroids in AE-IPF [37]. However, none of these observations comes from controlled studies [5, 10–12]. A large retrospective analysis of the clinical course of 461 IPF subjects did not show any significant impact of

 https://doi.org/10.1183/2312508X.10002017

steroid treatment on outcome in 90 patients who developed AE-IPF, regardless of dosage and scheme of administration [3].

Papiris *et al.* [41] performed a prospective noncontrolled study on the clinical course of 24 AE-IPF events in which withdrawal of any immunosuppressive therapy at admission was performed in association with the administration of best supportive treatment and broad-spectrum antibiotics. The authors reported overall 1- and 3-month survival of 52% and 45%, respectively, with longer survival in immunosuppressive-naive patients compared with treatment-experience patients (log-rank test, p=0.022). It should be noted that this study, rather than demonstrating a deleterious effect of steroid treatment during AE-IPF, underlined a negative prognostic role of steroid administration before AE-IPF onset [41].

With the lack of a clear demonstration of pathogenic differences between stable IPF and AE-IPF that can justify treatment changes, some authors have questioned the role of steroids in AE-IPF. Such drugs may even have harmful effects, increasing susceptibility to microbes [42]. Large well-designed clinical studies are needed to provide stronger evidence in favour of or against steroid use in AE-IPF. Steroid therapy in AE-IPF has often been associated with various types of immunosuppressant agents, although no recommendation has been given by current guidelines in favour or against any of them [43].

Cyclosporine A and tacrolimus

Cyclosporine A (CsA) and tacrolimus are immunosuppressant agents often used in the treatment of allotransplant recipients and in collagen vascular diseases [44]. These drugs inhibit phosphatase calcineurin, an intracellular protein that is able to activate nuclear factor of activated T-cells (NF-AT) transcription factor, downregulating the expression of several genes involved in the inflammatory response, such as IL-2, IL-6 and interferon-γ [45].

It has been demonstrated that CsA inhibits transforming growth factor-β-induced signalling *in vitro* and collagen deposition in human lung fibroblasts [46]. Based on this evidence, CsA has been proposed as a potential modulator of lung fibrotic processes. However, only a few reports with controversial results are available about the use of CsA in AE-IPF [13–15].

In 2003, Inase *et al.* [13] retrospectively reviewed the clinical course of 13 AE-IPF patients, seven of whom received CsA at a dosage of 1–2 $mg \cdot kg^{-1} \cdot day^{-1}$ after pulse therapy with high-dose *i.v.* corticosteroids, followed by oral tapering. The authors observed longer survival in the CsA-treated subjects.

Homma *et al.* [14] performed a retrospective analysis of the clinical course of 33 patients with various progressive interstitial lung diseases, including nine with AE-IPF, treated with CsA (50–200 $mg \cdot day^{-1}$) plus corticosteroids. The survival of CsA-treated AE-IPF subjects was significantly higher when compared with an historical reference cohort of 35 untreated subjects.

Sakamoto *et al.* [15] reviewed the medical records of 22 autopsied AE-IPF cases, 11 of whom received steroid therapy (methylprednisolone 1 $g \cdot day^{-1}$ for 3 days, followed by maintenance of 0.5–1 $mg \cdot kg^{-1} \cdot day^{-1}$) concomitant with CsA. The authors found a significantly longer survival in the CsA group than in the non-CsA group.

Table 1. Pharmacological agents evaluated for the treatment of AE of IPF (AE-IPF)

Agent	Putative mechanisms of action	Study design (treated patients n)	Scheme of administration	Outcome	First author [ref.]
Corticosteroid monotherapy	Suppression of cellular and humoral immunity Reduction of pro-inflammatory cytokines	Case series (3)	MP 1 g·day^{-1} for 3 days, followed by a tapered dosage based on physiological response	Survival from 5 months to 2.5 years	Kondoh [9]
		Retrospective, noncontrolled (17)	Not specified	Overall mortality=24/25 (96%)	Al-Hameed [5]
		Retrospective, noncontrolled (58)	MP 1 g·day^{-1} for 3 days, followed by a tapered dosage (some patients also treated with cyclophosphamide, % not specified)	Overall mortality=25/54 (46%) MST=23 days (range 3–114 days)	Akira [10]
		Retrospective, noncontrolled (9)	HC 0.5–1 g·day^{-1} for 3 days, rapidly tapered and discontinued within 4 weeks	3-year survival=42.5%	Suzuki [11]
		Retrospective, noncontrolled (13)	High dose, not further specified; occasionally associated with other treatments (*e.g.* cyclophosphamide, PMX-DHP)	3-month mortality=69%	Tachikawa [12]
Other immunosuppressants [#]					
Cyclosporine A (CsA)	Calcineurin inhibitor Inhibition of TGF-β-induced collagen deposition	Retrospective, case–control (7)	1–2 mg·kg^{-1}·day^{-1}	1- and 3-month survival in CsA *versus* non-CsA group=100% *versus* 83% and 71% *versus* 33%, respectively; overall survival range=4–276 *versus* 2–66 weeks	Inase [13]

Continued

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Table 1. Continued

Agent	Putative mechanisms of action	Study design (treated patients n)	Scheme of administration	Outcome	First author [ref.]
		Retrospective, case–control (9)	50–200 mg·day^{-1}	MST in CsA *versus* non-CsA group=9.9 *versus* 1.7 months (log-rank test, p<0.01)	Homma [14]
		Retrospective, controlled (11)	100–150 mg·day^{-1}	Mortality in CsA *versus* non-CsA group=7/11 (64%) *versus* 10/11 (91%) MST=285 *versus* 61 days (log-rank test, p<0.01)	Sakamoto [15]
Tacrolimus	Calcineurin inhibitor Inhibition of TGF-β-induced collagen deposition 100 times more potent than CsA	Retrospective, controlled (5)	Continuous *i.v.* administration for 5–14 days (target serum level=20 ng·mL^{-1}), followed by oral administration (target serum level=5 ng·mL^{-1})	Overall survival in tacrolimus *versus* non-tacrolimus group=4/5 (80%) *versus* 1/10 (10%) MST >92 *versus* 38 days (log-rank test, p<0.05)	Horita [16]
Cyclophosphamide	Cytotoxic alkylating agent with anti-inflammatory properties	Retrospective, noncontrolled (10)	500 mg *i.v.*, increased by 200 mg every 2 weeks, maximum=1500 mg in single dose, providing WBC >3000 cells·mm^{-3}	1- and 3-month survival=100% and 55%, respectively	Morawiec [17]
		Case series, noncontrolled (11)	600 mg·m^{-2} of BSA monthly; maximum=1000 mg in a single dose	3-, 6- and 12-month survival=73%, 63% and 55%, respectively	Novelli [18]
		Retrospective (32)	*i.v.* administration of ⩾100 mg·day^{-1}	Survival=9/32 (28%) Predictor of in-hospital mortality at multivariate logistic analysis (OR 3.17, 95% CI 1.10–9.15)	Oda [19]

Continued

Table 1. Continued

Agent	Putative mechanisms of action	Study design (treated patients n)	Scheme of administration	Outcome	First author [ref.]
Antibiotics[¶]					
Macrolides	Antibiotic with anti-inflammatory and immunomodulating properties	Prospective, open-label, controlled (20)	*i.v.* 500 mg day^{-1} azithromycin for 5 days	2-month survival in azithromycin *versus* fluoroquinolones group=4/20 (20%) *versus* 39/56 (70%) MST=not reached *versus* 29 days (log-rank test, p<0.001) Predictor of survival in Cox regression model (HR 0.21, 95% CI 0.07–0.59)	Kawamura [20]
		Retrospective (48)	Not mentioned	Survival=23/48 (48%) Predictor of survival at univariate (OR 0.28, 95% CI 0.13–0.61) and multivariate (OR 0.37, 95% CI 0.15–0.86) logistic analysis	Oda [19]
Cotrimoxazole	Antibiotic with anti-inflammatory and immunomodulating properties Possible reduction of neutrophil-derived oxidative stress	Retrospective (115)	400/80 mg tablets both at high dose (⩾6 tablets·day^{-1}, n=74) and at low dose (1–5 tablets·day^{-1}, n=41)	Survival=56/115 (49%) Predictor of survival at multivariate logistic analysis (OR 0.28, 95% CI 0.13–0.61) Possible dose-dependent effect	Oda [19]
PMX-DHP	Bactericidal and anti-inflammatory properties	Open-label pilot study (6)	One to five times·day^{-1} for 2–6 h, at a flow rate of 80–100 mL·min^{-1}	1-month survival=4/6 (67%)	Seo [21]

Continued

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Table 1. Continued

Agent	Putative mechanisms of action	Study design (treated patients n)	Scheme of administration	Outcome	First author [ref.]
	Removal of circulating endotoxins, pro-inflammatory cytokines, activated monocytes and neutrophils	Retrospective, noncontrolled (19)	Once daily for 4–6 h at a flow rate of 80 mL·min^{-1} repeated after 48 h	1-, 2- and 3-month survival=47%, 32% and 26%, respectively	Tachibana [22]
		Retrospective, noncontrolled (73)	Once daily for 2 consecutive days at a flow rate of 80–100 mL·min^{-1}	1- and 3-month survival=70% and 35%, respectively	Abe [23]
		Retrospective, controlled (14)	Long perfusion time administration (6–12 h·day^{-1})	12-month survival in PMX-DHP *versus* non-PMX-DHP group=48% *versus* 6% (log-rank test, p=0.041) More effective in more severe cases of disease (log-rank test, p=0.021) where it is a predictor of survival (HR 0.226, p=0.031)	Enomoto [24]
		Retrospective, controlled (27)	Once daily (6 h·day^{-1}) for 2 successive days at a flow rate of 80–100 mL min^{-1}	MST in PMX-DHP *versus* non-PMX-DHP group=192 *versus* 29 days 30- and 90-day survival=70% and 48%, and 63% and 26%, respectively (log-rank test, p=0.040) Predictor of survival at multivariate analysis (HR 0.44, 95% CI 0.22–0.87)	Oishi [25]

Continued

Table 1. Continued

Agent	Putative mechanisms of action	Study design (treated patients n)	Scheme of administration	Outcome	First author [ref.]
Human recombinant thrombomodulin (rhTM)	Anticoagulation *via* protein C activation Potential influence on both haemostatic and inflammatory pathways Administered in association with steroid therapy	Prospective, controlled (20)	0.06 mg·kg^{-1}·day^{-1}, diluted in 100 mL of sterile saline administered *i.v.* for 30 min for 6 days	28-day mortality in rhTM *versus* non-rhTM group=35% *versus* 83% (log-rank test, p=0.048)	Tsushima [26]
		Retrospective, controlled (16)	As above	3-month survival in rhTM *versus* non-rhTM group=69% *versus* 40%, (log-rank test, p=0.048)	Isshiki [27]
		Prospective, controlled (20)	As above	3-month survival in rhTM *versus* non-rhTM group=70% *versus* 35% (log-rank test, p=0.002) Independent predictor of survival in a multivariate analysis (OR 0.219, 95% CI 0.049–0.978)	Kataoka [28]
		Prospective, controlled (9)	As above	90-day mortality of AE-IPF and AE-NSIP=36% and 90%, respectively (p=0.023) MST of AE-IPF and AE-NSIP=not reached and 15 days, respectively (log-rank test, p=0.007) Subgroup analysis for IPF not reported	Abe [29]

Continued

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Table 1. Continued

Agent	Putative mechanisms of action	Study design (treated patients n)	Scheme of administration	Outcome	First author [ref.]
Plasma exchange (PEX) plus rituxmab	Reduction of circulating autoantibodies and total immunoglobulins plus depletion of B-lymphocytes	Open-label pilot study, controlled (7+4 treated with extended protocol)	1.5 times estimated plasma volume exchange daily for the first 3 days and, after a 24 h interval, for a further 2 days, plus *i.v.* rituximab 1 g weekly for subsequent 2 weeks Extended protocol includes IVIG administration	2-month and 1-year survival in PEX +rituximab *versus* non-PEX+rituximab (mean±SE)=55±15% *versus* 20±9%, and 46±15% *versus* 0%, respectively Predictor of mortality (HR 0.31, 95% CI 0.12–0.79)	Donahoe [30]
Sivelestat	Inhibitor of neutrophil elastase Some authors report better survival Evidence from a prospective study, not controlled	Prospective (10)		6-month survival=40%	Nakamura [31]

MP: methylprednisolone; MST: mean survival time; HC: hydrocortisone; PMX-DHP: polymyxin B-immobilised fibre column direct haemoperfusion; TGF-β: transforming growth factor-β; *i.v.*: intravenous; WBC: white blood cell; BSA: body surface area; HR: hazard ratio; AE-NSIP: AE of nonspecific interstitial pneumonia; IVIG: intravenous immunoglobulins. #: administered in association with steroids; the rationale for their use is their role in interfering with immunity and inflammatory host response, but this is not addressed by current guidelines; ¶: often broad-spectrum and empirical, co-administered with high-dose steroid treatment; procalcitonin-guided antibiotic therapy did not show a difference in survival or day of hospitalisation.

Tacrolimus (FK-506) has an *in vitro* immunosuppressant activity 100 times greater than that of CsA, together with a powerful antifibrotic activity [47, 48]. *In vitro* studies have demonstrated that it inhibits not only NF-AT intracellular signalling, but also the activation cascade of nuclear factor-κB, preventing immune activation *via* two different intracellular pathways [49].

The potential role of tacrolimus in treating AE-IPF was underlined by Horita *et al.* [16], who retrospectively evaluated five patients treated with continuous *i.v.* tacrolimus infusion for 5–14 days, followed by oral treatment, in association with conventional methylprednisolone pulse therapy with slow tapering. The authors reported a difference in survival ratio and duration between the patients treated with tacrolimus plus steroid and the 10 AE-IPF steroid-treated controls. Major side-effects of combined therapy were observed in three out of the five patients, but none of them died from these complications. In contrast, four out of the 10 control subjects died from reported steroid side-effects.

In order to limit systemic side-effects of such immunosuppressive treatments without reducing their immunomodulating efficacy in the targeted organs, a new lung-specific delivery strategy using engineered nanoparticle inhalation has been proposed [50]. Tacrolimus inhalation through microparticles has shown promising effects in a murine model of bleomycin-induced lung fibrosis [51, 53]. A CsA inhaled formulation for pulmonary delivery has also been developed, but studies in experimental models of lung fibrosis are lacking [53].

Cyclophosphamide

Cyclophosphamide is a cytotoxic alkylating agent, studied extensively in scleroderma lung disease, that depresses the inflammatory response through suppression of lymphokine production and lymphocyte functional modulation [54, 55].

The IPF international working group recently reported on four studies involving a total of 128 AE-IPF cases treated with cyclophosphamide, whose outcomes are difficult to interpret due to the heterogeneity of the studies and the absence of any control groups [37].

Morawiec *et al.* [17] performed a retrospective analysis of 10 Caucasian AE-IPF subjects treated with a combined regimen of high-dose pulse steroids, followed by cyclophosphamide. The authors reported a 3-month survival of 55%.

More recently, in 2016, Novelli *et al.* [18] retrospectively reviewed a case series of 11 AE-IPF patients treated with high-dose pulse steroids, followed by cyclophosphamide administration. The authors reported 3-, 6- and 12-month survival of 73%, 63% and 55%, respectively. They also reported the development of treatment-related nonlethal adverse events in three patients. It is possible that these survival rates may have been influenced by the contemporary administration of continuous positive airway pressure in four of the 11 patients, an additional intervention with potential effects on the clinical course of AE-IPF.

In the same year, Oda *et al.* [19] published a large epidemiological study on prognostic factors in severe rapidly progressive IPF patients treated with high-dose steroid therapy and mechanical ventilation. In this study, high-dose *i.v.* cyclophosphamide administration ($\geqslant$100 mg·day^{-1}) was associated with poor prognosis, together with advanced age, in a multivariate logistic analysis.

 https://doi.org/10.1183/2312508X.10002017

Taken together, the available evidence is not strong enough to support the use of cyclophosphamide in AE-IPF patients. The adequate dosage protocol remains unknown, but high dosages appear to exert deleterious effects.

Currently, an RCT exploring the efficacy of *i.v.* cyclophosphamide plus corticosteroid in AE-IPF treatment is ongoing (ClinicalTrials.gov, trial number NCT02460588). The experimental dosage is 600 $mg \cdot m^{-2}$ every 2 weeks for the first two doses, followed by 600 $mg \cdot m^{-2}$ monthly (maximal dose of 1.2 g), with dosage adjustments based on age and renal function. The results of this study will provide good-quality evidence in favour of or against the use of this drug as an add-on therapy for AE-IPF.

Antibiotics

Generally in AE-IPF, an empirical broad-spectrum antibiotic treatment is administered, even in the absence of a bacterial isolate. IPF guidelines have highlighted the need to exclude infections in the diagnostic assessment of AE-IPF [43]. This is not always feasible, as there is often the need for invasive procedures with a non-negligible risk of morbidity in subjects with critical respiratory conditions.

To date, there has been no controlled study assessing the beneficial effects of empirical antibiotic treatment in AE-IPF. The only available RCT on this topic compares clinician-determined *versus* procalcitonin (PCT)-guided antibiotic treatment [56]. In the interventional arm of this study, empirical antibiotics were administered in the case of a PCT level above the serum threshold of 0.25 $ng \cdot mL^{-1}$ and were maintained until serum PCT levels fell below this threshold. Although the PCT-guided approach resulted in a shorter antibiotic treatment duration (8.7±6.6 *versus* 14.2±5.2 days; $p<0.001$) and reduced the number of treated subjects (25 out of 33 *versus* 35 out of 35; $p<0.001$), no significant difference was found in terms of success rate, mortality or duration of mechanical ventilation [56].

Limited evidence suggests that the administration of azithromycin or cotrimoxazole may have positive effects on AE-IPF [9, 19, 20, 57].

Shulgina *et al.* [58] reported that cotrimoxazole, in addition to the standard treatment for stable IPF, resulted in a reduction of all-cause mortality. In a large retrospective study on rapidly deteriorating IPF, cotrimoxazole treatment was identified as a protective factor for survival in both univariate and multivariate logistic regression, with a dose-dependent effect [19]. Huie *et al.* [59] investigated the potential role of *Pneumocystis jirovecii* infection, a bacterium treated with cotrimoxazole as the first-line therapy, in the exacerbation of respiratory symptoms in IPF. The role of cotrimoxazole in AE-IPF may be due to its anti-inflammatory effects, in addition to its antimicrobial activity [60, 61]. Macrolide treatment has also been associated with a lower risk of mortality in AE-IPF because of its possible anti-inflammatory and immunomodulating properties [19]. A prospective open-label study with historical controls reported that patients with AE-IPF treated with *i.v.* azithromycin had significantly longer survival than patients treated with fluoroquinolones [20]. Azithromycin represented an independent prognostic predictor in a Cox proportional regression model adjusted for potential confounders [20].

Recently, Kuse *et al.* [57] retrospectively evaluated the effect of long-term macrolide administration (erythromycin or clarithromycin) in IPF patients on mortality and AE-IPF incidence, reporting a better 60-month survival rate (log-rank test, $p=0.047$), a lower

incidence of AE-IPF (13.8% *versus* 34.8%) and a significantly longer AE-free survival rate (log-rank test, p=0.02) compared with the nontreated group.

Although the studies discussed have various limitations, they suggest a potential beneficial effect of the use of macrolide and cotrimoxazole on AE-IPF prevention and outcome.

Regarding the role of antiviral treatments, various studies have reported evidence of heterogeneous viral infections during AE-IPF, such as parainfluenza virus, rhinovirus, coronavirus, torque teno virus, Epstein–Barr virus (EBV), respiratory syncytial virus, cytomegalovirus (CMV), measles virus and various herpesviruses [62–65]. A new viral infection or the re-activation of latent viral infection could be responsible for an immune stimulation burdening the acute worsening of the underlying disease [64].

To date, there has been no trial examining the use of antiviral therapy in AE-IPF. The only available data come from a 2011 open-label pilot study on *i.v.* ganciclovir treatment in 14 advanced IPF patients with serological evidence of current or past EBV infection who failed standard treatments, including steroids, azathioprine and cyclosporine. This study did not investigate the incidence of AE-IPF, but reported a mortality of six out of 14 patients during a 12-month follow-up, and lung transplantation in five of the 14 patients [66]. Currently, there is an ongoing registered pilot single-centre RCT on oral administration of valganciclovir 900 $mg \cdot day^{-1}$ for 12 weeks in IPF patients with serological evidence of current or past EBV/CMV infection, which will explore AE-IPF incidence as a secondary end-point (ClinicalTrials.gov, trial number NCT02871401).

Polymyxin B-immobilised fibre column direct haemoperfusion

The polymyxin B (PMX)-immobilised fibre column direct haemoperfusion (PMX-DHP) cartridge is a device for extracorporeal haemoperfusion developed in 1984 consisting of PMX-linked polystyrene–chloroacetamide methyl fibres chemically immobilised through covalent bonds.

The first clinical use of PMX-DHP was reported in sepsis [67], where it showed bactericidal and anti-inflammatory properties, binding circulating endotoxins and selectively reducing the number of activated monocytes and neutrophils, resulting in a reduction of the circulating pro-inflammatory, pro-fibrotic and pro-angiogenic cytokines and reactive oxygen species (ROS) [68, 69]. These results provide the rationale for the use of PMX-DHP in AE-IPF [70].

Seo *et al.* [21], in an open-label pilot study published in 2006, reported that four out of six patients with AE-IPF who required mechanical ventilation survived >30 days after PMX-DHP treatment, suggesting a clinical benefit of PMX-DHP. In 2011, Tachibana *et al.* [22] reported survival rates of 47% at 1 month, 32% at 2 months and 26% at 3 months in 19 AE-IPF patients treated with PMX-DHP. In 2012, Abe *et al.* [23] performed a large retrospective multicentre study including 73 patients with AE-IPF, reporting a significant improvement in PaO_2/inspired oxygen fraction (FIO_2) ratio (205.4±122.1 *versus* 173.9±105.4 Torr (mean±SD); p<0.001) since the first PMX-DHP treatment, with 1- and 3-month survival of 70% and 35%, respectively.

In 2015, Enomoto *et al.* [24] retrospectively reviewed 40 AE-IPF events in 31 patients, 14 of whom (20 events) were treated with PMX-DHP with a long perfusion time, reporting a better 12-month survival in the PMX-DHP group. Stratifying the patients according to the

 https://doi.org/10.1183/2312508X.10002017

severity of stable disease, subjects with severe IPF showed a significantly longer survival if treated with PMX-DHP, while in milder disease, PMX-DHP did not seem to add significant benefit [24]. In a recent Cox proportional hazard analysis, PMX-DHP was a significant predictor of survival [25]. Moreover, it seems that the time from AE-IPF onset to PMX-DHP administration is a significant predictor of survival [25].

Larger studies are needed to confirm the role of PMX-DHP treatment in AE-IPF patients and to understand more fully the mechanisms underlying these effects.

Oral anticoagulant, heparin and recombinant human thrombomodulin

It is well known that inflammation, fibrosis and coagulation share some molecular pathways [71, 72], and various authors have reported a state of hypercoagulability in AE-IPF lungs [26]. On this basis, it has been postulated that pharmacological modulation of coagulation and fibrinolysis could have potential therapeutic effects, influencing both haemostatic and inflammatory pathways.

In 2005, Kubo *et al.* [73] published a prospective open-label RCT on anticoagulants in hospitalised IPF patients with various degrees of respiratory deterioration. Anticoagulation was reached using low-weight heparin during hospitalisation and oral warfarin at hospital discharge to maintain an international normalised ratio of between 2 and 3. The authors reported a significant reduction in mortality in the anticoagulant arm (15 deaths in 21 exacerbations *versus* two deaths in 11 exacerbations; Fisher's exact test, p=0.008), but failed to demonstrate that anticoagulation could reduce the incidence of AE-IPF [73].

Some authors have raised concerns about the validity of these results because of the low retention rate and the possibility of selection bias, as the sample was recruited during hospitalisation with high AE-IPF incidence [74]. Currently, the validity of such findings is also questionable because of the concomitant use of steroids, a treatment no longer administered in stable IPF [8, 43]. In 2013, Tomassetti *et al.* [75], in a retrospective study, did not confirm these results.

A double-blinded RCT on warfarin treatment in IPF was stopped early, in 2006, after an interim analysis demonstrated an excess of mortality in the warfarin arm compared with placebo (14 *versus* three deaths; hazard ratio (HR) 4.85, 95% CI 1.38–16.99; p=0.005), mainly due to respiratory causes (exacerbation or progression) [76]. Based on this trial, anticoagulation is no longer supported in stable IPF. There is currently no conclusive evidence in favour of or against anticoagulation in AE-IPF [43].

Another potential pharmacological agent interfering in coagulative processes in AE-IPF is soluble recombinant human thrombomodulin (rhTM). TM is a transmembrane protein expressed by endothelial cells, which acts as a cofactor binding thrombin in order to enhance the activation of protein C and reduce thrombin-mediated clotting, resulting in anticoagulant and anti-inflammatory effects [77–80]. RhTM has been approved for the treatment of disseminated intravascular coagulation in Japan.

In 2015, Tsushima *et al.* [26] performed a prospective controlled study in which 20 AE-IPF patients under mechanical ventilation were treated with rhTM and compared with six untreated AE-IPF patients. The study showed a significant reduction in 28-day mortality in the treated patients with a rapid improvement of SaO_2/FIO_2 ratio in survivors from the first

day of treatment. Following this study, other investigators have used the same rhTM dosage, duration and frequency of administration [27, 29, 81].

Also in 2015, Kataoka *et al.* [28] published a prospective case–control study reporting a significantly longer 3-month survival among 20 AE-IPF patients treated with rhTM in association with a high-dose steroid pulse, cyclosporine, empirical antibiotics and noninvasive ventilation (NIV), compared with 20 historical control subjects who received the same therapeutic interventions except for rhTM. The role of rhTM therapy as an independent determinant for survival was confirmed by a multivariate analysis [28].

In the same year, Isshiki *et al.* [27] published a single-centre retrospective study on the clinical course of 16 AE-IPF patients treated with rhTM plus steroid pulse compared with 25 control patients treated with steroids only. The authors reported a significantly higher 3-month survival in the rhTM group. Notably, the control group in this study showed a significantly higher baseline D-dimer level, possibly indicating that a worse coagulative imbalance was present [27].

Abe *et al.* [29] showed that *i.v.* rhTM treatment significantly improved the 3-month survival in patients with AE-IPF and AE of nonspecific interstitial pneumonia in comparison with nontreated patients: rhTM administration was identified as an independent predictor of survival at 90 days in a multivariate analysis.

More recently, Hayakawa *et al.* [81] reported a difference in the 28-day survival between 10 AE-IPF patients treated with 380 $U \cdot kg^{-1}$ rhTM plus steroid therapy and 13 historical controls (70% *versus* 54%, respectively), which became significant at 1 year (median survival time 153 *versus* 48 days; log-rank test, p=0.04).

A multicentre phase III RCT evaluating the efficacy, safety and superiority of 380 $U \cdot kg^{-1} \cdot day^{-1}$ *i.v.* rhTM infusion *versus* placebo in addition to standard steroid therapy for AE-IPF is currently ongoing (ClinicalTrials.gov, trial number NCT02739165).

Plasma exchange plus rituximab

The rationale for the use of rituximab plus plasma exchange is evidence of circulating autoantibodies and B-lymphocyte abnormal function in the pathogenesis of IPF [82–84].

An open-label trial on the feasibility and safety of combined plasma exchange plus rituximab treatment in association with conventional high-dose steroid therapy in AE-IPF is ongoing (ClinicalTrials.gov, trial number NCT01266317). The experimental protocol consists of 1.5 times estimated plasma volume exchange daily for the first 3 days and, after a 24 h interval, for a further 2 days, plus *i.v.* rituximab 1 g weekly for the subsequent 2 weeks. This treatment has been identified as an independent prognostic factor with a better 2-month (55±15% *versus* 20±9% (mean±SE), HR 0.35, 95% CI 0.13–0.98; p=0.035) and 1-year (46±15% *versus* 0%, HR 0.31, 95% CI 0.12–0.79; p=0.009) survival in a pilot study, which is part of this trial [30].

Sivelestat

Sivelestat is a pharmacological agent discovered in 1991 in Japan, where it is approved for the treatment of ARDS and systemic inflammatory response syndrome [85, 86]. It is an inhibitor of neutrophil elastase, an enzyme that acts both to degrade various extracellular

 https://doi.org/10.1183/2312508X.10002017

proteins, including collagen, elastin, immunoglobulins and lung surfactant proteins, and to stimulate the production of inflammatory cytokines [87, 88].

NAKAMURA *et al.* [31] published a prospective study on 10 invasively ventilated AE-IPF patients treated with sivelestat plus high-dose methylprednisolone pulse, followed by oral maintenance. They reported a 6-month survival of 40% and a significantly higher PaO_2/FIO_2 ratio in survivors after 7 days from the start of therapy. These promising results need to be confirmed in further larger trials.

Nonpharmacological supportive therapies

Oxygen, mechanical ventilation and newer approaches

AE-IPF patients generally require hospital admission and supplemental oxygen therapy to obtain a PaO_2 >60 mmHg. According to the guidelines, oxygen therapy is administered to stable IPF patients with respiratory failure, and there is no evidence against supplemental oxygen administration during AE-IPF [8].

The current guidelines recommend against the use of mechanical ventilation in advanced IPF patients with respiratory failure because of its poor prognostic impact (short-term mortality of up to 90% in AE-IPF ventilated patients) and its potentially harmful effects due to barotrauma and ventilator-associated infections [4, 5, 8, 89–92].

Post-surgical exacerbations of IPF seem to have a better prognosis than idiopathic ones, and should be recognised and treated early, as they could be more responsive to mechanical ventilation and other life-support treatments [89, 93, 94].

FERNÁNDEZ-PÉREZ *et al.* [91] reported a survival of 40% in a cohort of IPF patients with respiratory failure, 70% of whom were admitted after surgical procedures.

Recently, studies reassessing the prognosis of invasively ventilated AE-IPF patients in the light of new ventilation strategies have suggested that invasive mechanical ventilation should not be systematically denied, but should be discussed on a case-by-case basis, particularly in view of potential future therapeutic options, such as lung transplant [95, 96].

As evidence supporting the guidelines has been obtained from studies mainly involving invasively ventilated patients, the role of NIV is still debated [97]. A large retrospective cohort study showed that the in-hospital mortality of IPF patients receiving NIV was significantly lower than that of invasively ventilated patients (30.9% *versus* 51.6%; p<0.0001) [96].

VIANELLO *et al.* [98] performed an observational retrospective analysis on short-term mortality in 18 IPF patients treated with NIV for acute respiratory failure, six of whom were classified as AE-IPF. They reported that four AE-IPF patients were successfully treated with NIV, defining success as the avoidance of endotracheal intubation, discharge from the ICU and survival with preserved consciousness for at least 48 h after being transferred to the respiratory ward. Overall, survival was significantly longer in the NIV-success group than in the NIV-failure group (median survival time 90.0 *versus* 18.0 days; p=0.0001) [98]. This study raised some objections regarding the poor QoL of NIV-treated IPF patients and NIV efficacy in prolonging survival in view of transplantation options [99]. Other authors

who have observed different survival rates in NIV compared with invasively ventilated patients object that this outcome may be influenced by different baseline disease severities [6]. The NIV approach in the AE-IPF setting seems to provide some benefits in terms of relief from dyspnoea [100, 101], although evidence from large high-quality RCTs is required.

NIV may also have prognostic implications. SUZUKI *et al.* [102] found that the lack of P_{aO_2}/F_{IO_2} ratio improvement with positive end-expiratory pressure (PEEP) seemed to be predictive of short-term mortality in a multivariate Cox proportional hazard model (HR 3.23, 95% CI 1.50–6.9; p=0.003). There is little information regarding the best ventilator setting [103]. A lung-protective strategy borrowed from ARDS treatment with a low/moderate tidal volume (5–8 $mL \cdot kg^{-1}$) is preferable [104]. Although the optimal PEEP level in AE-IPF is unknown, high pressures are not commonly used, as they have been correlated with alveolar overdistention, lung injury and poor prognosis in a condition where alveolar recruitment is potentially low [91, 98, 105]. However, some authors have reported administration of a maximum median PEEP of 10 cmH_2O [81, 101]. A high respiratory rate and permissive hypercapnia may be needed. A comparison between continuous positive airway pressure and NIV with spontaneous/timed mode showed no significant outcome differences in nontachypnoeic and nonhypercapnic patients, although the number of reported cases was very limited [101]. Further studies are needed.

Based on this evidence, the decision to refer AE-IPF patients to the ICU is still much debated and should be made cautiously on a case-by-case basis, considering the potential benefits in term of prognosis and future therapeutic options, the patient's values and preferences, and the risk of inappropriate overtreatment.

An emerging role has recently been given to high-flow nasal cannula oxygen administration, which seems to provide some therapeutic and palliative benefits, both in reducing the work of breathing and in ameliorating oxygenation through different mechanisms: the rise in pressure amplitude of breathing cycles and mean pressure, the decrease in breathing rate and the CO_2 washout effect in the upper airway anatomical dead space [106]. This technique requires less training than NIV and may be more acceptable and more broadly applied outside the ICU environment, although the evidence supporting its use is based mainly on case reports and retrospective observational data [107, 108].

Extracorporeal membrane oxygenation has been reported in rare cases as a bridge to transplantation [109, 110]. Recently, VIANELLO *et al.* [111] reported the successful management of a case of acute respiratory failure in acute worsening of IPF refractory to NIV through a pump-assisted veno-venous system for extracorporeal CO_2 removal, although no similar reports are currently available.

Palliative care

The unpredictable evolution of IPF makes it desirable to have an early discussion with patients about end-of-life care preferences [43, 112, 113]. Despite this, few patients actually undergo end-of-life discussions [114]. Palliation of dyspnoea, cough, pain and anxiety is part of the general supportive management of AE-IPF and should not be neglected by clinicians because of fear of drug-related side-effects. Palliation is generally obtained with opioid and benzodiazepine administration [115].

 https://doi.org/10.1183/2312508X.10002017

Prevention of AE-IPF

Prevention of AE-IPF is desirable in the clinical management of IPF, as no treatment has demonstrated proven benefits on AE-IPF prognosis, which remains very poor. The main strategy is to avoid or treat potential triggers of lung injury. Some evidence suggests that IPF treatments may be able to prevent AE-IPF. The precise mechanism is still not fully known; as low FVC is a known risk factor for AE-IPF [3, 116], it is possible that slowing the functional decline through current antifibrotic treatments may result in an indirect reduction of the risk of developing AE. It has also been hypothesised that antifibrotic treatments may be able to directly reduce lung susceptibility to various triggers [117].

Triple combination therapy with prednisone, azathioprine and *N*-acetylcysteine in stable IPF should no longer be administered, as it has been associated with a higher risk of death, hospitalisation and AEs [118].

The potential role of macrolides in AE-IPF prevention has been described in a previous section in this chapter.

Antifibrotic agents

Nintedanib is an approved therapeutic agent for stable IPF: it is an indolinone derivative, and acts as an inhibitor of various tyrosine kinases [119], including fibroblast growth factor receptor, vascular endothelial growth factor receptor and platelet-derived growth factor, involved in the abnormal fibroproliferative processes in IPF lungs (table 2) [128–130]. The double-blinded, phase II RCT TOMORROW (To improve pulmonary fibrosis with BIBF-1120) assessed the efficacy and safety of nintedanib at four different oral dosages in stable IPF, showing a positive effect on FVC decline [120]. In this trial, AE-IPF occurrence and recurrence over a time frame of 52 weeks were analysed as secondary end-points. The TOMORROW trial reported a significantly lower percentage of patients who experienced at least one AE-IPF event (risk ratio (RR) 0.16, 95% CI 0.003–0.7; p=0.01) in the nintedanib high-dosage arm (150 mg twice daily) and a significantly lower annual occurrence of AE-IPF per patient (RR 0.22; 95% CI 0.056–0.88; p=0.03) in comparison with placebo [120].

Two subsequent concurrent phase III RCTs evaluating the efficacy and safety of nintedanib at a fixed dosage of 150 mg twice daily *versus* placebo (INPULSIS-1 and -2) confirmed the significant reduction in functional deterioration in IPF patients, although they showed mixed and controversial results regarding the effects on AE-IPF [121]. In INPULSIS-1, there was no significant difference between the nintedanib and placebo arms in the proportion of patients with at least one investigator-reported AE-IPF event (6.1% and 5.4%, respectively) and in time to the first AE-IPF (HR 1.15, 95% CI 0.54–2.42) [121]. The INPULSIS-2 trial showed a significant delay in the time to first AE-IPF event (HR 0.38, 95% CI 0.19–0.77; p=0.005) and a lower proportion of patients with at least one investigator-reported AE-IPF event (3.6% *versus* 9.6%, respectively) in the nintedanib arm compared with the placebo arm [121]. A pre-specified sensitivity analysis of pooled data from the INPULSIS trials demonstrated a 68% reduction in the risk of a central committee-adjudicated confirmed/suspected AE-IPF with nintedanib therapy [121]. A *post hoc* pooled analysis of data from the TOMORROW and INPULSIS trials showed a lower incidence of at least one AE-IPF event in nintedanib-treated subjects (4.6% *versus* 8.7%, respectively) with a significantly longer time to the first investigator-reported AE-IPF event

(HR 0.53, 95% CI 0.34–0.83; p=0.004) compared with placebo [122]. These results are consistent with other published results [131], and highlight the potential role of nintedanib in preventing AE-IPF.

Collard *et al.* [132] recently analysed data on AE-IPF events from the INPULSIS trials, reporting a trend for lower 1-, 3- and 9-month mortality in hospitalised patients for both investigator-reported and committee-adjudicated suspected/definitive AE-IPF treated with nintedanib in comparison with nontreated patients. Although this result suggests a potential beneficial impact of nintedanib on post-AE-IPF survival, it should be interpreted with caution as the number of events was relatively small [132].

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is the first approved drug in Europe for IPF treatment, exerting multiple and still not fully elucidated actions, including inhibition of profibrotic and pro-inflammatory cytokines and suppression of ROS (table 2) [105, 124, 133].

The CAPACITY (Clinical studies assessing pirfenidone in idiopathic pulmonary fibrosis: research of efficacy and safety outcomes) 1 and 2 and ASCEND (Assessment of pirfenidone to confirm efficacy and safety in idiopathic pulmonary fibrosis) RCTs showed that pirfenidone is able to reduce functional respiratory decline and prolong progression-free survival in IPF [125, 134, 135]; however, the effect on AE-IPF was not evaluated in these trials.

In another double-blinded RCT evaluating the efficacy of pirfenidone in IPF, AE-IPF occurred in 14% of placebo-treated patients in comparison with no report of AE-IPF

Table 2. Proposed agents with a potential preventative role in AE of IPF (AE-IPF)

Agent	Role	First author [ref.]
Nintedanib	Intracellular inhibitor of various tyrosine kinase; approved for IPF treatment Longer time to first AE-IPF and reduced frequency of AE-IPF in one of two trials Reduced incidence at pooled data Evidence from RCT	Richeldi [120–122]
Pirfenidone	Pleiotropic molecule with antifibrotic, anti-inflammatory and antioxidant activity; approved for IPF treatment Some authors reported lower AE-IPF incidence, but not confirmed by others Evidence from RCTs	Azuma [123]; Taniguchi [124]; Noble [125]
Macrolide	Antibiotic with anti-inflammatory activity Long-term treatment associated with low AE-IPF incidence and longer AE-IPF-free time Evidence from retrospective controlled study	Kuse [57]
Antacid therapy	Higher incidence of gastro-oesophageal reflux disease in IPF patients Reduction of incidence, with both proton pump inhibitor and histamine H_2 blockers Evidence from *post hoc* analysis of placebo arms of three RCTs	Lee [126]
Lifestyle	Pneumococcal and influenza vaccination Reduction of air pollution exposure	Song [3]; Richeldi [117]; Johannson [127]

 https://doi.org/10.1183/2312508X.10002017

among pirfenidone-treated patients (p=0.003), leading to an early interruption of the trial after 9 months [123].

A multicentre, double-blinded RCT carried out by Taniguchi *et al.* [124] involving 275 IPF patients treated with high-dose (1800 mg·day^{-1}) and low-dose (1200 mg·day^{-1}) pirfenidone *versus* placebo showed a lower vital capacity decline and a longer progression-free survival over 52 weeks, but did not confirm the results of the study by Azuma *et al.* [123] regarding AE-IPF incidence.

A meta-analysis of these RCTs did not show a significant effect of pirfenidone on AE-IPF (RR 0.59, 95% CI 0.19–1.84), although the quality of this evidence was low because the collected data came from indirect composite outcomes [136].

According to this cumulative evidence, the efficacy of pirfenidone in AE-IPF prevention is still debated. An exception seems to be represented by pre-operative administration for lung cancer surgery [137].

Prevention of post-surgical AE-IPF

Various studies have reported the development of acute respiratory deterioration after pulmonary and nonpulmonary surgery, video-assisted thoracoscopy and bronchoscopy in IPF patients [138].

Multiple mechanisms are involved in AE-IPF after surgical procedures, including ventilator-induced acute mechanical stretch stress, hyperoxia, fluid overload and direct surgical lung injury. Lung-protective ventilation strategies, a strict fluid balance and post-operatory monitoring may be considered to avoid the development of AE-IPF. Excessive oxygen administration both in peri- and post-operative settings should be avoided because of the risk of enhancing ROS production, thus contributing to redox imbalance and lung injury [104]. Pirfenidone may help to prevent post-surgical AE-IPF [138].

Anti-reflux therapy

Gastro-oesophageal reflux (GOR) is one of the risk factors for IPF and AE-IPF, probably due to GOR-related microaspiration of acid (*e.g.* gastric acids) or alkaline (*e.g.* pepsin, bile salts) gastric content, often occult, that may trigger a lung inflammatory reaction [139, 140]. Treatment with antacids may prevent GOR-related lung injury and the consequent stimulus for fibroproliferation (table 2). In a case–control study, Lee *et al.* [126] reported that pepsin levels, a marker of gastric aspiration, were significantly higher in bronchoalveolar lavage of AE-IPF patients compared with stable controls (p=0.04). Noth *et al.* [141] showed that IPF patients have a higher prevalence of hiatal hernia, a predisposing condition for GOR, compared with patients with other respiratory diseases. A *post hoc* analysis of the placebo arms of three RCTs on the use of various therapeutic agents for stable IPF showed that patients routinely treated with antacids (proton pump inhibitors or histamine H_2 blockers) were less likely to develop AE-IPF than patients not taking antacids (p=0.05) [126]. Based on this evidence, antacid therapy has been suggested as a potentially effective intervention to prevent AE-IPF.

New perspectives in preventative drugs

A recent *post hoc* multivariate analysis of the placebo arms of three RCTs revealed that statin therapy is associated with lower respiratory-related hospitalisation (HR 0.44, 95% CI 0.25–0.80; p=0.006) and IPF-related mortality (HR 0.36, 95% CI 0.14–0.95; p=0.04) [142]. Although in this study AE-IPF incidence was not specifically investigated, this evidence could stimulate future studies focusing on the potential preventative role of these drugs.

Lifestyle

Some lifestyle behaviours are recognised as potential risk factors for developing AE-IPF (table 2). As infections may be involved in AE-IPF pathogenesis, it may be useful to reduce the risk of infection through preventative strategies, such as influenza and pneumococcal vaccination [117], although there are some reports on AE-IPF after pandemic influenza vaccination [143]. Smoking is a controversial preventative factor, as a large retrospective study reported that never having smoked was a risk factor for AE-IPF [3]. Measures to control air pollution may also have a role in reducing the risk of AE-IPF, as demonstrated by Johannson *et al.* [127], who reported that increased ozone and nitrogen dioxide exposure is associated with the risk of developing AE-IPF.

Conclusion

AE-IPF represents an acute, unpredictable, life-threatening event whose pathogenesis is still not fully elucidated and that has a serious impact on the overall survival of IPF patients. Available treatment strategies are currently supported by low-quality evidence, and there is an urgent need for RCTs exploring the efficacy and safety of pharmacological and nonpharmacological approaches. The relatively low incidence of both IPF itself and its AEs makes it difficult to design clinical studies with adequate power and sample size to explore the effects on mortality of experimental treatments. The lack of RCTs exploring the effects of each intervention on AE-IPF makes it difficult to generalise results obtained from small observational noncontrolled studies. The results of the available studies may also be influenced by bias in patient selection because of nonhomogeneity of the inclusion criteria, partly due to different definitions of AE-IPF. Finally, recruitment in clinical trials is also limited by technical difficulties in converging acutely ill patients from peripheral hospitals to tertiary research centres, as subjects with AE-IPF are often referred to the nearest healthcare facility. In this context, we believe that prevention is crucial. A better understanding of the pathogenic mechanisms of IPF itself and of AE-IPF will be the basis for future studies on new preventative strategies.

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Disclosures: L. Richeldi has received personal fees from Biogen, Sanofi-Aventis, Takeda, Shionogi, Cipla, Pliants Therapeutics, Boehringer Ingelheim and Roche, outside the submitted work.

Chapter 15

The role of pulmonary rehabilitation in the prevention of exacerbations of chronic lung diseases

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The prevention of exacerbations and hospital admissions is of major importance in the management of COPD. Various studies, including meta-analyses, have demonstrated that pulmonary rehabilitation programmes can reduce the risk of hospital readmission and may prevent future events. At present, the heterogeneity of studies and the small number of patients involved allows only a weak recommendation for pulmonary rehabilitation programmes to reduce exacerbations in patients at risk. This chapter speculates on the mechanisms through which these potential benefits are obtained. The targeted population, the optimal moment of pulmonary rehabilitation initiation and the multidisciplinary strategies that should be implemented are also discussed. Future studies that have been adequately designed and powered to study the effect of pulmonary rehabilitation programmes on the prevention of AEs are now needed.

Cite as: Rodrigues FM, Loeckx M, Troosters T, *et al.* The role of pulmonary rehabilitation in the prevention of exacerbations of chronic lung diseases. *In:* Burgel P-R, Contoli M, López-Campos JL, eds. Acute Exacerbations of Pulmonary Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 224–246 [https://doi.org/10.1183/2312508X.10016916].

In patients with chronic lung diseases, AEs are known to have an impact on disease symptoms, disease progression and prognosis. AEs are associated with reduced levels of physical activity, worsened peripheral muscle weakness, aggravated symptom burden and compromised QoL, and result in significant healthcare costs. As a result of their huge impact on many disease components, AEs and hospital admissions catalyse subsequent events, with rapid deterioration of the respiratory disease status and its concurrent morbidities. This vicious circle was nicely demonstrated in a Canadian cohort study, which found that the occurrence of a second severe AE was a crucial event within the disease's progression process, since it was associated with an exponential decline in health status and a 3-fold increase in risk for experiencing a subsequent AE [1]. In addition, AEs result in

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accelerated lung function decline [2] and are accompanied by an increased risk of mortality, particularly in the weeks following their occurrence [3–6]. Therefore, early identification, treatment and prevention of future events are fundamental components within the management of chronic lung diseases.

Comprehensive management of COPD aimed at preventing exacerbations comprises both pharmacological and nonpharmacological interventions. These approaches result in complementary effects and are typically combined.

One of the nonpharmacological treatment options that has been proposed to counteract this deleterious event is pulmonary rehabilitation [7]. According to the American Thoracic Society (ATS) and the European Respiratory Society (ERS), pulmonary rehabilitation is defined as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" [8]. This multidisciplinary treatment aimed at the modifiable nonrespiratory consequences of respiratory diseases has proved effective in improving functional capacity, exercise tolerance, muscle force, dyspnoea sensation and QoL, and in reducing the use of healthcare resources [9–11]. These important achievements are only possible by a multidisciplinary approach, which tackles the several interrelated components of disease management: pharmacotherapy optimisation, exercise training, smoking cessation, psychological support, nutritional and social counselling, education and self-management. Figure 1 summarises possible pathways and interrelationhips among pulmonary rehabilitation components and the prevention of AEs. However, the benefits of the prevention of AEs, hospital readmissions and mortality are less clear, due to the heterogeneity of the conducted trials and the limited numbers of patients involved [7]. Moreover, most of the rehabilitation studies were not designed to investigate the effect of pulmonary rehabilitation on AE as a primary outcome. These limitations translate to a reduced methodological quality in terms of accuracy on how AEs are defined and how they are prospectively monitored and statistically analysed. It is worth noting that most studies have only included patients who were hospitalised due to AE-COPD and only monitored the effect of pulmonary rehabilitation on moderate exacerbations (requiring antibiotics or corticosteroids) and severe exacerbations (requiring hospitalisation). The effect of pulmonary rehabilitation on mild events has been less well studied. Findings should therefore be interpreted with caution. Most studies that have investigated the role of pulmonary rehabilitation on risk for AEs (as assessed by emergency department visits and number of hospitalisation days due to AEs) were conducted in patients with COPD who were recruited for participation in a pulmonary rehabilitation programme during or immediately after an AE. The role of pulmonary rehabilitation in preventing AEs in patients with more stable COPD and long-term follow-up has been studied less extensively [12]. To the best of our knowledge, there are no studies that have looked at the effect of rehabilitation in chronic respiratory diseases other than COPD (*e.g.* interstitial lung disease, bronchiectasis, asthma), in which exacerbations are also considered to be critical targets for appropriate disease management.

The aim of this chapter is to provide an overview of the evidence of the effect of pulmonary rehabilitation on the prevention of AEs and hospital admissions in patients with COPD. We provide insight into how different components of pulmonary

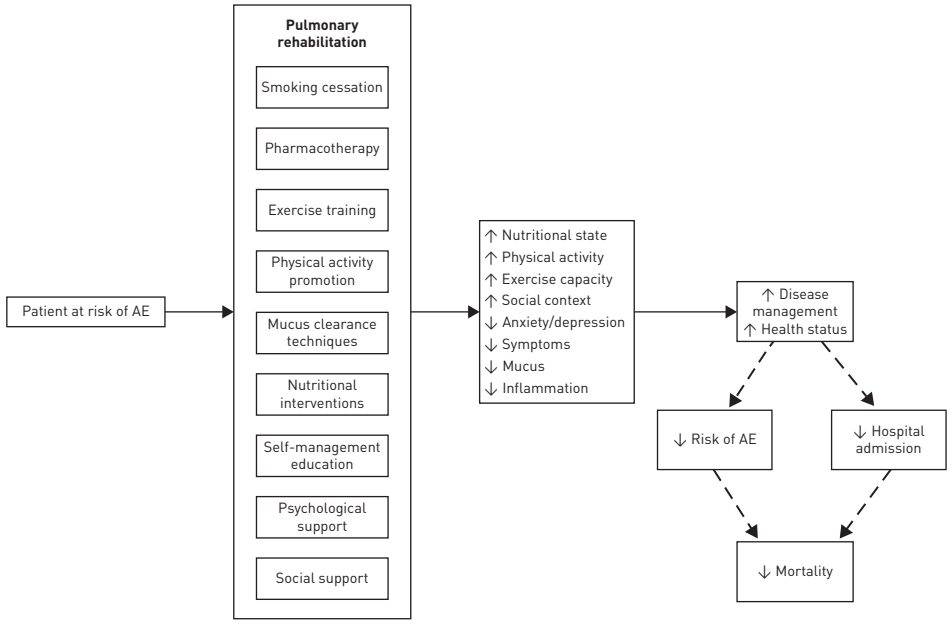

Figure 1. Summary of possible pathways and interrelationships among pulmonary rehabilitation components and the prevention of AEs.

rehabilitation may contribute to the observed benefits, and formulate some challenges for the future in this important area.

Effects of pulmonary rehabilitation on AE-COPD during the stable or exacerbated state

Pulmonary rehabilitation is usually offered during a more stable phase (normally delivered through outpatient or community-based programmes). Robust evidence also advocates rehabilitation initiated after an AE (initiated a few weeks after discharge). It is less clear whether rehabilitation should be offered or started during the index exacerbation to prevent subsequent exacerbations. Table 1 shows an overview of rehabilitation studies that have analysed the effect of pulmonary rehabilitation on exacerbations in patients within a stable setting or in patients immediately after an AE. The table describes the study design, the time point of pulmonary rehabilitation initiation, the number of patients included in the study, the number of patients randomised to the pulmonary rehabilitation group, the number of patients who completed pulmonary rehabilitation and performed the last evaluation, the period of follow-up and the significance of findings on the AE-related end-points. These data are based on the systematic reviews of Puhan *et al.* [7] and Moore *et al.* [12], which aimed to identify whether pulmonary rehabilitation reduces hospitalisation and emergency department visits for AEs in patients with COPD. A last literature search was performed for screening of possible updates. Only articles from which full text could be obtained were included in the table. Overall, completion rates or adherence to pulmonary rehabilitation in both stable and post-AE settings were sufficient (86% and 73%, respectively) to expect a potential benefit on AEs. Those studies investigating the effects

 https://doi.org/10.1183/2312508X.10016916

of pulmonary rehabilitation offered as part of the treatment of AEs, but without having any AE-related outcome, were not included.

In clinical practice, outpatient pulmonary rehabilitation mostly targets patients in a stable condition. The meta-analysis by MOORE *et al.* [12] included a specific subgroup analysis for stable patients, and a statistically significant reduction in the admission rate per patient-year was found after pulmonary rehabilitation when compared with the previous year (0.682, 95% CI 0.34–1.38, *versus* 1.988, 95% CI 1.26–3.14). This type of study design, however, might confer some bias to the results, as previous AEs could interfere with the probability of having new AE occurrences. The included interventions varied considerably in duration, frequency of sessions, type of exercises, inclusion of home exercise programmes and incorporation of education, and this heterogeneity prevented the performance of sensitivity analysis for "dose" effects of pulmonary rehabilitation. Moreover, it is not clear whether the AE prevention in stable patients was done at a primary level, avoiding the occurrence of a first AE, or whether patients were referred just after an AE with the aim of preventing recurrence. It is worth noting that the literature is generally based on hospitalisation as the outcome measure of exacerbations. Although admission is representative for more severe events with the highest cost expenditures [35], the ambulatory management of a less severe exacerbation also reflects an increased burden to the patient and may be beneficially influenced by pulmonary rehabilitation. Indeed, GUELL *et al.* [25] showed that, during 2 years of follow-up, the pulmonary rehabilitation group presented with significantly fewer exacerbations (3.7±2.2 *versus* 6.9±3.9 (mean±SD) per patient) compared with the controls, although there was no significant decrease in the number of hospitalisations (0.6±1.0 *versus* 1.3±1.8 per patient).

A recent Cochrane review by PUHAN *et al.* [7] investigated the effects of pulmonary rehabilitation in patients who were recruited after hospital admission for an AE. The review included 12 studies that conducted inpatient pulmonary rehabilitation programmes within 2–8 days of hospital admission and seven studies that initiated pulmonary rehabilitation after AE hospitalisation discharge (six outpatient and one home-based programme). Some studies presented a protective effect on hospital admissions and mortality compared with usual community care, while others did not. Overall, the studies led to a statistically significant effect of pulmonary rehabilitation on reducing hospital readmission, but, due to the heterogeneity of the studies, the authors concluded that new prospective studies are needed to investigate which setting of pulmonary rehabilitation programmes determines a true effect of rehabilitation on readmission. Moreover, targeting hospitalisation does not necessarily mean that observed benefits are truly related to the prevention of exacerbations, as many other factors, including comorbidities and social and environmental context, determine whether the patient will be hospitalised, although the latter factors are also influenced by the pulmonary rehabilitation programme.

In a recent ATS/ERS guideline on AE-COPD management [36], pulmonary rehabilitation is recommended from 3 weeks after hospital discharge based on its effect on hospital admissions and its improvements in QoL. Interestingly, a weak recommendation against rehabilitation initiated during hospitalisation was given based on weak evidence. This conditional recommendation was driven mainly by the increased mortality risk of pulmonary rehabilitation that was found by one large RCT [22]. In this study, 320 patients were randomised within 48 h of hospital admission either to usual care or to pulmonary rehabilitation, which was supervised during their hospital stay and extended after discharge with nonsupervised training until completion at 6 weeks. The methodology of this trial has

Table 1. Studies investigating the effects of pulmonary rehabilitation in AE-related end-points

First author [ref.]	Time point of pulmonary rehabilitation initiation	Study design	Included patients n	Patients allocated to pulmonary rehabilitation group n	Patients finishing pulmonary rehabilitation n	Patients from pulmonary rehabilitation group included in analysis n	Time to final evaluation (months)	AE-related outcomes	Significance of ⩾1 of the AE-related outcomes
Acute setting[#]									
Nava [13]	3–5 days after ICU admission, when clinically stable	RCT	80	60	NA	41	Discharge	Total length of stay in respiratory ICU for AE-COPD and mortality	NS
Behnke [14]	In hospital, when clinically stable	RCT	26	14	NA	13	18	Number of AE-COPD-related hospital admissions per patient and inhalation of β_2-agonists	*
Man [15]	Within 10 days of hospital discharge	RCT	42	21	18	18	3	Hospital readmissions rate (%), accident and emergency department visits rate (%) and total hospitalisation days	*
Boxall [16]	Home-based intervention in house-bound patients	RCT	60	30	23	23	6	Proportion of patients with AE-COPD-related hospital admissions and average length of stay at readmission	*
Murphy [17]	At hospital discharge	RCT	31	16	13	13	6	Number of patients who experienced AE-COPD (defined as an increase in breathlessness, wheezing or cough and a change in sputum colour and tenacity)	NS

Continued

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Table 1. Continued

First author [ref.]	Time point of pulmonary rehabilitation initiation	Study design	Included patients n	Patients allocated to pulmonary rehabilitation group n	Patients finishing pulmonary rehabilitation n	Patients from pulmonary rehabilitation group included in analysis n	Time to final evaluation (months)	AE-related outcomes	Significance of ⩾1 of the AE-related outcomes
Eaton [18]	During hospitalisation, as soon as medically appropriate	RCT	97	47	39	39	3	Number of AE-COPD-related hospital readmissions per patient, time to first AE-COPD-related readmission, number of inpatient days	NS
Seymour [19]	Within 1 week of hospital discharge	RCT	60	30	23	23	3	Proportion of patients with AE-COPD-related hospital readmissions, proportion of patients with AE-COPD-related emergency department attendances, median time to any event	*
Ko [20]	2–3 weeks after hospital discharge	RCT	60	30	22	22	12	Number of AE-COPD per patient (requiring treatment with a course of oral steroids or antibiotics), number of AE-COPD-related admissions per patient, number of accident and emergency department visits per patient	NS
Revitt [21]	Within 4 weeks of hospital discharge	Before and after pulmonary rehabilitation	160	160	100	155	12	Number of hospital days and hospital admissions to respiratory and medical wards	*
Greening [22]		RCT	389	196	148	196	12	Number of patients with ⩾1 (all-cause)	NS

Continued

Table 1. Continued

First author [ref.]	Time point of pulmonary rehabilitation initiation	Study design	Included patients n	Patients allocated to pulmonary rehabilitation group n	Patients finishing pulmonary rehabilitation n	Patients from pulmonary rehabilitation group included in analysis n	Time to final evaluation (months)	AE-related outcomes	Significance of ⩾1 of the AE-related outcomes
	Within 48 h of hospital admission							readmissions, number of (respiratory-related) admissions per patient, time to first (all-cause and respiratory-related) readmission, total number of (all-cause) hospitalisation days and mortality	
Ko [23]	2–3 weeks after hospital discharge	RCT	180	90	NA	73	12	Number of AE-COPD per patient (requiring treatment with a course of oral steroids or antibiotics), number of AE-COPD-related admissions per patient, number of accident and emergency department visits per patient, length of hospital stay for AE	*
Total			1185	694		616			
Stable setting[¶]									
Foglio [24] (COPD and asthma)	No exacerbation in the 4 weeks before the study	Before and after pulmonary rehabilitation	71	61	NA	51	12	Number of hospital admissions and AE-COPD (requiring change of usual medication and prescription of	*

Continued

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Table 1. Continued

First author [ref.]	Time point of pulmonary rehabilitation initiation	Study design	Included patients n	Patients allocated to pulmonary rehabilitation group n	Patients finishing pulmonary rehabilitation n	Patients from pulmonary rehabilitation group included in analysis n	Time to final evaluation (months)	AE-related outcomes	Significance of ⩾1 of the AE-related outcomes
								systemic steroids and/or antibiotics)	
Guell [25]	No exacerbation or hospitalisation in the previous month	RCT	60	30	24	24	24	Number of AE-COPD (defined by either increased dyspnoea or dry or productive cough, whether sputum was purulent or not) and AE COPD-related hospitalisations	*
Rubi [26]	No worsening of clinical condition in the previous month	Before and after pulmonary rehabilitation	82	82	72	67	12	Number of exacerbations (any sustained increase of baseline symptoms that required a modification of management or treatment) and AE-COPD-related hospitalisations and length of hospital stay	*
Total			213	173		142			
Unclear setting[+]									
Hui [27]	NA	Before and after pulmonary rehabilitation	42	42	36	36	12	Number of AE-COPD-related hospital admissions and length of hospital stay	*
Golmohammadi [28]	NA	Before and after pulmonary rehabilitation	210	210	185	139	12	Costs of emergency visits and length of hospital stay for respiratory causes	*

Continued

Table 1. Continued

First author [ref.]	Time point of pulmonary rehabilitation initiation	Study design	Included patients n	Patients allocated to pulmonary rehabilitation group n	Patients finishing pulmonary rehabilitation n	Patients from pulmonary rehabilitation group included in analysis n	Time to final evaluation (months)	AE-related outcomes	Significance of ⩾1 of the AE-related outcomes
Cecins [29]	Referrals predominantly from outpatient clinics and private physicians	Before and after pulmonary rehabilitation	256	256	187	187	12	Number of hospital admissions AE-COPD and total bed-days (calculated by adding bed-days from all admissions)	*
Rasekaba [30]	Referrals from general practitioners, external medical specialists, acute hospital service during emergency department presentation or inpatient admission	Cohort study	53	53	29	29	12	Emergency department presentations, inpatient admissions, admission length of stay and cumulative acute care costs for admission	*
Liu [31]	NA	RCT	132	36	33	32	6	Number of AE-COPD-related hospital admissions	NS
Román [32]	NA	RCT	97	33	16	15	12	Number of AE-COPD-related hospital admissions, AE-COPD-related visits to family physician, and AE-COPD-related treatments with antibiotics or corticosteroids	NS
Major [33]	NA	Cohort study	170	118	78	78	12	Rate of respiratory-related (cough, wheezing, breathlessness,	*

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Table 1. Continued

First author [ref.]	Time point of pulmonary rehabilitation initiation	Study design	Included patients n	Patients allocated to pulmonary rehabilitation group n	Patients finishing pulmonary rehabilitation n	Patients from pulmonary rehabilitation group included in analysis n	Time to final evaluation (months)	AE-related outcomes	Significance of ⩾1 of the AE-related outcomes
Nguyen [34]	NA	Cohort study	1081	558	NA	558	12	pneumonia, bronchitis, or AE-COPD) emergency department visits and hospital admissions Number of COPD-related emergency department visits and hospitalisations	*
Total			2041	1306		1074			
Total from all settings			3439	2173		1832			

Division is made according to the time point of pulmonary rehabilitation initiation. Information is provided regarding the type of study design, the number of patients included in the study, those allocated to pulmonary rehabilitation and those who completed pulmonary rehabilitation, and the time to final evaluations, the investigated outcomes and the significance of AE-related outcomes. 1 month was considered to be 4 weeks. NA: information not available. *: significant difference ($p<0.05$) in favour of the pulmonary rehabilitation group; NS: nonsignificant difference ($p>0.05$) (*i.e.* a significant difference ($p<0.05$) in favour of the control group). #: studies in which patients were included during a hospital stay and up to 4 weeks after hospital discharge. ¶: studies in which patients were included if they were free from any AE or hospitalisation for at least 4 weeks. +: studies in which it was not clear whether patients were recruited in an acute or stable setting; however, most of these studies are more likely to have included patients in a stable setting. Table based on systematic reviews [7, 12], including an updated literature search. Only articles from which full text could be obtained were included in the present table.

been profoundly debated, as patients in the intervention group only participated in an average of 2.6 supervised pulmonary rehabilitation sessions [7, 37, 38]. Therefore, it was argued that the observed mortality was only representative of an inconsistent unsupervised programme at a moment of increased risk.

Components of pulmonary rehabilitation and their role in AE prevention

The multidisciplinary nature of pulmonary rehabilitation aims to improve a patient's general clinical condition from different perspectives. The classic components of a rehabilitation programme comprise optimisation of pharmacotherapy, including adherence to the prescribed therapy, smoking cessation support, exercise training, improvement of self-management skills when needed, psychological counselling, occupational therapy, provision of social support and nutritional therapy. Based on the multidisciplinary approach, an individualised programme is constructed that offers the appropriate components to the appropriate patients.

Some of the individual components may, directly or indirectly, reduce the risk of AEs. Patients referred to pulmonary rehabilitation programmes typically accumulate risk factors for exacerbations. These include older age, active smoking, poor lung function, a history of previous exacerbation, inappropriate pharmacotherapy or underprescription of long-term oxygen therapy, lack of physical activity, poor functional capacity, poor QoL and health status, higher levels of anxiety and depressive mood status, gastro-oesophageal reflux and chronic bronchitis with increased mucus production [39–43]. Many of these risk factors are tackled through components of a rehabilitation programme. It is therefore no surprise that, overall, pulmonary rehabilitation programmes have been shown to be effective in preventing exacerbations of COPD. There is no doubt that smoking cessation has the greatest potential in influencing the natural history of the disease [43]. However, the other elements of pulmonary rehabilitation are also essential in the management of chronic respiratory diseases. Although it is difficult to compare the relative weight of each of these components in terms of decreasing the risk of future AEs, we will provide an overview of the mechanisms that are potentially involved.

Smoking cessation

Smoking cessation, an important component and outcome of pulmonary rehabilitation, is known to be the most efficient intervention in improving the health status and the rate of lung function decline in patients with COPD [44, 45]. A study by Au *et al.* [46] with a large cohort of 23 971 subjects demonstrated its effectiveness in decreasing the risk of AEs when compared with patients who continued smoking, with the duration of the tobacco-free period also influencing the outcome. The authors stated that the removal of a potent stimulant of the inflammatory response (*i.e.* smoking) might explain their findings [46]. However, smoking cessation is not a simple and straightforward achievement. The frequency of successful smoking cessation is low, and relapse rates are high [47]. A recent Cochrane review concluded (based on high-quality evidence) that a combination of behavioural treatment and pharmacotherapy is effective in helping smokers with COPD to quit [48]. Furthermore, smoking cessation programmes can be successfully combined within the pulmonary rehabilitation setting. A nonrandomised trial by Paone *et al.* [49] showed that implementing a smoking cessation programme as part of pulmonary

 https://doi.org/10.1183/2312508X.10016916

rehabilitation increased the rate of continuous abstinence from 32% to 68% compared with smoking cessation as a stand-alone treatment. In this regard, persistent smoking behaviour may not exclude patients from rehabilitation programmes, as the latter may offer a window for a more successful attempt.

Pharmacotherapy

Vaccinations and optimal pharmacotherapy, as well as ensuring a correct inhalation technique, are essential in chronic respiratory disease management. Long-acting bronchodilators, inhalation corticosteroids and their combinations are known to reduce the risk of AEs in patients with COPD [50]. The adherence to inhaled medication is also significantly associated with a reduced risk of hospital admission due to exacerbations [51]. Besides its direct effect on the risk reduction of AEs, optimising and tailoring individual pharmacotherapy strategies during pulmonary rehabilitation may also improve endurance of higher training loads and facilitate greater improvements in exercise capacity [52]. Although different studies with combination therapy of long-acting anticholinergics and β_2-agonists show significant increases in exercise tolerance, there is no consistent evidence suggesting that these gains in lung function and exercise capacity are translating into more physical activity during daily life [53–56]. Any indirect effect of pharmacotherapy on AEs through the optimisation of patients' physical fitness and subsequent daily activity is therefore unsure. Further details on the evidence and mechanisms of optimal pharmacological treatments for the prevention of AEs can be found in other chapters of this *Monograph* [57–61].

Exercise training

To date, no study has clearly demonstrated a direct link between exercise training and the risk reduction of future exacerbations in COPD. Conversely, there is also no evidence that participation in exercise training programmes increases susceptibility to developing an exacerbation.

Endurance and strength training are key components of any rehabilitation strategy and are known to induce physiological adaptations in muscle function, muscle morphology and metabolism, even in patients with more severe disease [62]. A tailored exercise training programme improves the oxidative capacity and efficiency of the muscles, which leads to a reduction in fatigue and a smaller ventilatory demand for a given exercise intensity [63–65]. By reducing the severity of dyspnoea and fatigue sensation, a longer endurance for moderate to intense daily physical activities might be achieved with a potential anti-inflammatory effect. Nevertheless, the (anti-)inflammatory effects of exercise training in patients with COPD are not fully understood and conflicting results have been reported. For instance, Rabinovich *et al.* [66] found an abnormal increase in a circulating inflammatory marker (TNF-α) in patients after a single bout of exercise, even at the end of an 8-week training programme, which was not observed in the healthy controls. These data did not corroborate findings from our group that high-intensity cycling exercises did not increase the circulating levels of inflammatory markers, as measured by CRP, IL-6 and CXCL8 in COPD patients, in both exacerbated and stable clinical states [67].

A recent Cochrane review also could not determine whether exercise in the general population is effective for altering the occurrence, severity and duration of acute respiratory

infections, due to the small sample sizes, risk of bias and population heterogeneity across studies [68]. Nevertheless, there is evidence suggesting that moderate-intensity exercise improves immune function and potentially reduces the risk and severity of respiratory viral infections, whereas high-intensity exercise leads to the opposite changes in healthy adults [69]. This should be taken into consideration when prescribing exercise to respiratory patients, especially for the most frail, who may also need more monitoring to ensure adequate exercise prescription and evolution.

Finally, it is well known that COPD is a heterogeneous disease with comorbidities such as cardiovascular and peripheral diseases, obesity, osteoporosis and diabetes, which might arise from the disease itself or from common risk factors such as smoking, ageing and physical inactivity [70]. Exercise training can positively influence these risk factors and improve the burden of comorbidities [71–74], which may indirectly reduce hospitalisation risk.

Physical activity

Caspersen *et al.* [75] defined physical activity as "any bodily movement produced by skeletal muscles that results in energy expenditure". Patients with chronic respiratory disease are less physically active in comparison with their healthy peers [76–78]. Physical inactivity is known as a catalyst of major health debilitating disease processes in both the healthy population and in patients with chronic respiratory diseases [79, 80]. Besides increasing the risk of all-cause mortality [81–83], physical inactivity is known to be independently associated with hospital admissions for AEs in patients with COPD after adjustment for some relevant confounders [82, 83]. The occurrence of AEs might pave the way for a further reduction in physical activity, thereby increasing the risk for future AEs. We showed that patients who regained physical activity immediately after an AE were less likely to be readmitted to hospital [84]. It is tempting to speculate that this relationship is causal. Collectively, the data suggest a potential protective effect of physical activity on the risk of experiencing an AE. At the very least, pulmonary rehabilitation attempts to promote the long-term adherence to health-enhancing behaviours, including physical activity [8]. However, the latter objective has proven difficult to achieve, and the important benefits of exercise capacity after pulmonary rehabilitation are not automatically translated into a more active lifestyle [85]. A considerable proportion of patients return to their previous inactive life patterns from before rehabilitation, which might be one of the factors explaining the loss of the acquired benefits from pulmonary rehabilitation. A change in behaviour is necessary to maintain a high functional status and physical activity level. According to a recent meta-analysis, adding physical activity counselling to pulmonary rehabilitation might result in a higher increase in physical activity compared with pulmonary rehabilitation alone [86]. To the best of our knowledge, no study has provided evidence on the long-term improvements in physical activity after pulmonary rehabilitation or on its association with risk reduction of AEs [87]. Furthermore, studies that have investigated the beneficial effects of physical activity programmes have not reported on their effect on AEs, as none of them had exacerbation as a primary outcome [88–90].

Mucus clearance techniques

Patients with chronic respiratory diseases often experience excessive mucus in their airways (especially during AEs), which may be difficult to expectorate, creating an excellent breeding ground for bacteria, leading to future infections. Chronic mucus production is

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also associated with an accelerated decline in lung function [91, 92], increased risk of mortality [93–95] and reduced QoL [96–98]. Exercise training may have a direct effect on mucus clearance. Increasing ventilation and respiratory flow, with higher shearing forces along the airway walls [99, 100], may improve spontaneous mucus evacuation and reduce a patient's susceptibility to infections with respiratory viruses and pathogenic bacteria. Besides aerobic exercise, specific mucus clearance techniques, such as active cycles of breathing, autogenic drainage, and positive and oscillatory expiratory pressure applications, are indicated for hypersecretive patients [101] and may directly reduce the risk of infections. These mucus clearance techniques all aim to facilitate the clearance of excessive mucus that is present in the airways by applying physical forces to the chest, positive expiratory pressure to the airways (chest physiotherapy) or *via* adjustments of the patient's positioning (postural drainage). However, evidence of the effect of these techniques on AEs and their long-term benefits are unclear in both COPD subjects and in patients with bronchiectasis [102, 103]. A Cochrane review revealed that airway clearance techniques are safe to use in patients with COPD, but no prospective trials have provided evidence for the use of manual chest physiotherapy techniques during and after AEs [104]. However, most of the studies did not investigate the effects within subgroups of patients with an excess of mucus or a problem with expectoration, who are more likely to benefit from airway clearance techniques [102].

Nutritional interventions

Another factor that is commonly linked to disease progression, increased risk of exacerbations, hospitalisations and mortality is malnutrition [105, 106]. This is defined as a depletion in fat-free mass, and can occur even when the body weight is normal [107]. Malnutrition is prevalent in patients with advanced respiratory diseases, as there is an imbalance between metabolic demands and energy uptake. Patients with COPD have increased energy expenditure due to the increased work of breathing. Moreover, the perception of dyspnoea and several hormonal disturbances decrease appetite and diminish the nutritional intake, giving rise to a negative energy balance and cachexia [108]. To tackle this malnutrition and muscle wasting state, a Cochrane review concluded that nutritional supplementation is able to improve body weight, respiratory muscle strength, walking and QoL, especially in those patients who were malnourished [109]. Despite AE not being included as an outcome, an indirect protective effect might be extrapolated, according to the authors [109]. However, to date, no direct benefit of nutritional supplementation on the prevention of AEs has been established [109]. During hospitalisation for AE, the addition of nutritional intervention of balanced amounts of protein, fat and carbohydrate was shown to be feasible and tended to increase the body weight in those patients with involuntary weight loss from 2 to 4 months prior to hospitalisation [110]. Indeed, 47% of included patients presented involuntary weight loss, which raises the question of starting supplementation at its early signs for preventing hospitalisation. During the hospital stay, optimising a patient's intake may reduce this catabolic response of the systemic glucocorticoid treatment, inactivity, hypoxia and the increase in the systemic inflammatory response. The food selection is also important, as, for example, a diet high in carbohydrates is thought to increase the relative metabolic production of carbon dioxide and so increase the respiratory demand in COPD patients [105]. Finally, sufficient intake of essential components, such as vitamin D or a diet with isoflavones and polyunsaturated fatty acids, may also affect exacerbation risk by their direct anti-inflammatory effect [111, 112].

Self-management education

Self-management programmes are often described as components of rehabilitation, but it can be difficult to draw a line between self-management programmes and "rehabilitation". An International Expert Group recently agreed on a definition of COPD self-management intervention as: "structured but personalised and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour (s) and develop skills to better manage their disease. The ultimate goals of self-management are: a) optimising and preserving physical health; b) reducing symptoms and functional impairments in daily life and increasing emotional well-being, social well-being and QoL; and c) establishing effective alliances with healthcare professionals, family, friends and community. The process requires iterative interactions between patients and healthcare professionals who are competent in delivering self-management interventions. These patient-centred interactions focus on: 1) identifying needs, health beliefs and enhancing intrinsic motivations; 2) eliciting personalised goals; 3) formulating appropriate strategies (*e.g.* exacerbation management) to achieve these goals; and if required 4) evaluating and re-adjusting strategies. Behaviour change techniques are used to elicit patient motivation, confidence and competence. Literacy sensitive approaches are used to enhance comprehensibility" [113].

Patients' coping strategies and adaptations to their symptoms play an important role in the management and progression of the disease. Therefore, education should be implemented within pulmonary rehabilitation to provide patients with tools to overcome barriers, increase self-efficacy and enhance their knowledge of the disease. Providing self-management intervention is a way of empowering patients to adopt effective actions in handling their disease and may play an important role within the prevention plan for AEs [114, 115]. A self-management programme that included weekly visits for teaching and a single supervised exercise session at home, followed by unsupervised sessions, reduced the number of hospital admissions for AEs, emergency department visits and unscheduled physician visits by 39.8%, 41% and 58.9%, respectively [115]. The educational component was based on patient-friendly workbooks, which consisted of topics on disease aetiology, treatment strategies, and breathing and relaxation techniques. It also included an action plan in case of the occurrence of an AE. It should be mentioned that a similar approach has been adopted by others, who, despite an increase in QoL and shortened recovery time after AEs, were not able to demonstrate a risk reduction for future AEs [114]. A more recent study by Benzo *et al.* [116] also found positive results with a comprehensive health coaching intervention, which was based on motivational interviewing techniques delivered *via* the telephone and included a written action plan for AEs and an exercise prescription. The absolute risk of COPD-related hospitalisations was significantly decreased at 1, 3 and 6 months after hospital discharge, with a range of eight to 13 patients needed to treat to prevent one hospital admission. The action plan was noted as a key factor within the disease self-management in the study by Trappenburg *et al.* [114], as when patients were able to identify and react to an exacerbation, although not prevent it, its impact on health status and symptoms decreased and recovery was accelerated. It is important to note is that this intervention included the ongoing support of a case manager, which is the case when this is implemented in the pulmonary rehabilitation setting. However, an action plan delivered without close follow-up might be less effective, or even deleterious, as seen in the results of Fan *et al.* [117]. Their action plan intervention, delivered outside the rehabilitation setting, was not able to achieve a behavioural change, and patients did not initiate their action plan sooner than patients in the control group. Furthermore, the mortality rate was higher in the intervention group and

 https://doi.org/10.1183/2312508X.10016916

the study was interrupted. Despite not having a satisfactory explanation for this unexpected outcome, the authors mentioned that one different aspect of their intervention was the lower contact frequency between patients and case managers [117].

Psychological support

Next to its important role within the process of smoking cessation, providing psychological support to improve patients' emotional condition is also a direct aim of pulmonary rehabilitation. The definition of pulmonary rehabilitation also explicitly states that the goal of pulmonary rehabilitation is to enhance physical and psychological well-being. Anxiety and depression are very common comorbidities in COPD [118], and it is recognised that the reduction in exercise capacity may be related to psychological morbidity [8]. In turn, anxiety and panic can lead to emergency department visits and even to respiratory failure due to alterations in breathing patterns that often result in severe progressive dynamic hyperinflation [119]. While it has not been studied whether specific psychological interventions such as cognitive behavioural therapy or tackling anxiety may reduce the likelihood of unexpected readmissions, it is plausible that this may offer benefits to selected patients, particularly when combined with appropriate self-management strategies.

Social support

The last key component of pulmonary rehabilitation is its social component. Poor social status has been associated with nonadherence to pharmacotherapy in patients with COPD [120]. In the same study, exacerbations were associated with lower educational levels and low income [120]. While no study has prospectively found a direct link between improved social interactions and the prevention of AEs, it seems clear that patients who lack social support and are more socially deprived comprise a group of patients that merit special attention. Increasing the patients' level of participation and stimulating their social engagements remains an important patient-reported outcome and indicator of QoL for patients with chronic respiratory disease [121]. Disease progression, including the occurrence of AEs, results in avoidance of participation in activities, and this in turn may have an impact on patients' social networks and stimulate social isolation [122]. Pulmonary rehabilitation provides a safe environment in which patients can establish social connections with other patients and find professional advice, allowing them to engage again with family and friends. Furthermore, a social worker can offer advice for optimal access to different services that patients can access during an AE to prevent hospital admission.

Cost-effectiveness of pulmonary rehabilitation

Prevention of AEs is crucial due to their detrimental effects on a patient's health status and to the significant economic impact they impose on society. Griffiths *et al.* [123] described the cost-effectiveness of a multidisciplinary pulmonary rehabilitation programme in the UK in 200 patients with chronic respiratory diseases, mainly COPD. They measured the net cost directly borne by the health services and by the patients themselves, and contrasted it with the benefits gained by adding pulmonary rehabilitation to the standard care. The latter was measured by the quality-adjusted life-years (QALYs), which is an estimative of both quality and quantity of life lived, following healthcare interventions. The study showed that the cost/QALYs ratio was situated within a cost-effective range and that the addition of

pulmonary rehabilitation to standard care in patients with chronic respiratory diseases can result in financial benefits [123]. Another study by the same group focused on the effects of pulmonary rehabilitation on the use of healthcare resources within 1 year [124]. Despite not finding a difference in the number of patients admitted to hospital at least once between the pulmonary rehabilitation and standard care groups, the study found a decrease in days spent in hospital (reductions in both frequency and duration of respiratory-related admissions) in the pulmonary rehabilitation group compared with the standard care group. Patients who followed pulmonary rehabilitation also had a lower risk of mortality [124].

Accessibility and future of pulmonary rehabilitation

Despite its established benefits, most patients who would benefit from pulmonary rehabilitation never make it into the training programme for various reasons (*e.g.* transport, lack of motivation/knowledge, functional disability, distance) [125–127]. According to published data, only 0.9–1.4% of patients with moderate to severe disease attended pulmonary rehabilitation in Australia, the UK, Canada and New Zealand, and the major reasons were difficulties with transport such as parking and availability of public transport, mobility, distance and location of the programme [128]. These numbers are expected to be even smaller in countries with less developed economies. A large survey study highlighted the wide variability that exists among pulmonary rehabilitation programmes across the world [129]. As the objective of pulmonary rehabilitation to prevent exacerbations in a population at risk is dependent on patients' participation, major efforts are needed to overcome these barriers. While pulmonary rehabilitation can be a potent intervention in the prevention and treatment of AEs, it is clear that the intervention is underused. An ATS/ERS policy statement has set specific goals to promote further implementation of pulmonary rehabilitation and tackle the common barriers [130]. One of these barriers, the distance between the patient's home and the pulmonary rehabilitation centre, might be overcome by telerehabilitation programmes, which allow coaching and training from a distance [131, 132]. However, their effectiveness, safety and feasibility have only been established in small [133] or short-term [134–136] trials. Whether frail patients at risk for exacerbations are suitable candidates for remote rehabilitation programmes remains an open question. The ATS/ERS statement on pulmonary rehabilitation underlines the need for large-scale trials demonstrating the (cost-)effectiveness of these telerehabilitation programmes in comparison with conventional pulmonary rehabilitation programmes [8]. Tailoring of the programme, including the use of interactive (*e.g.* Nintendo Wii) and easy-to-use tools to maintain the patients' motivation, is deemed necessary in long-term telerehabilitation trials. Attention must be paid to the attitude of both patients and healthcare providers towards technology, as this might influence its effectiveness [137]. For example, modules that incorporate components of self-management (*i.e.* monitoring symptoms for early identification of AEs), physical activity promotion (*i.e.* stepcounters) and coaching (*i.e.* action plans) may be useful tools to reduce AEs and the risk of hospital admissions.

Conclusion

The prevention of exacerbations and hospital admissions is of major importance in the management of COPD. Various studies have demonstrated that pulmonary rehabilitation programmes reduce the risk of readmission and may also prevent future events. However,

 https://doi.org/10.1183/2312508X.10016916

the heterogeneity and small number of patients involved in studies included in meta-analyses allow only a weak recommendation for pulmonary rehabilitation programmes to reduce exacerbations in patients at risk. Nevertheless, most evidence indicates a high likelihood that pulmonary rehabilitation will have an impact on the severity of exacerbations and on healthcare costs. Furthermore, many components in the multidisciplinary approach of pulmonary rehabilitation carry the potential to affect exacerbations by direct or indirect pathways. Future studies should disentangle these mechanisms in more depth to address the most important components. In particular, interventions enhancing self-management strategies seem promising tools to reduce the burden of hospital admissions. In COPD patients prone to exacerbations, the large benefits of pulmonary rehabilitation on symptom burden, skeletal muscle function, exercise tolerance and QoL are still the main reason for referral. However, more powerful evidence on the risk reduction of AEs will strengthen the indication of pulmonary rehabilitation and justify a broader implementation.

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Acknowledgements: The authors would like to thank David Ruttens (University Hospital Leuven, Leuven, Belgium) for his scientific input into this chapter.

Disclosures: F.M. Rodrigues is funded by The National Council for Scientific and Technological Development (CNPq), Brazil (249579/2013-8). T. Troosters is supported by the Flemish Research Foundation (FWO) (#G.0871.13). W. Janssens is Senior Clinical Investigator of the FWO and is supported by the AstraZeneca Chair in Respiratory Diseases.

 https://doi.org/10.1183/2312508X.10016916